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Part VI

Department of Health and Human Services

Food and Drug Administration

Soda Water; Standard of Identity, and—Caffeine; Deletion of GRAS Status, Proposed Declaration That No Prior Sanction Exists, and Use on an Interim Basis Pending Additional Study; Proposed Regulations

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 165

[Docket No. 80N-0439]

Soda Water; Amendment to Standard

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) proposes to amend the standard of identity for soda water to accomplish the following: (1) Designate kola nut extract, rather than caffeine from this extract or from other extracts that naturally contain caffeine, as the mandatory ingredient in "cola-" and "pepper-" type soda water beverages; (2) provide for decaffeinated "cola" or "pepper" soda water beverages under the standard of identity; (3) continue to permit the use of added caffeine in these beverages as an optional ingredient.

DATES: Comments must be received on or before December 22, 1980.

ADDRESS: Written comments, data, or information to the Dockets Management Branch (formerly the Hearing Clerk's office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: F. Leo Kauffman, Bureau of Foods (HFF-214), Food and Drug Administration, 200 C St., SW, Washington, DC 20204, 202-245-1164.

SUPPLEMENTARY INFORMATION: The current standard of identity for soda water (21 CFR 165.175) describes "cola-" and "pepper-" type soda water beverages as follows:

> * * * Soda water designated by any name which includes the word 'cola' or 'pepper' shall contain caffeine from kola nut extract and/or other natural caffeine-containing extracts. Caffeine may also be added to any soda water. The total caffeine content in the finished food shall not exceed 0.02 percent by weight * * *

The intent of the current standard is to require caffeine from kola nut extract or other natural sources as a mandatory ingredient in "cola-" or "pepper-" type soda waters and to allow added caffeine in these beverages as an optional ingredient. The standard sets the upper limit on the total amount of caffeine that may be present—both naturally occurring and added—at 0.02 percent by weight. The standard does not set a minimum amount of naturally occurring or added caffeine that must be present.

In conjunction with its review of the safety of caffeine as an added ingredient in food (the results of which are discussed in a notice of proposed rulemaking published elsewhere in this issue of the **Federal Register**, FDA has reviewed the standard of identity for soda water to determine whether the provisions of the standard relating to caffeine remain appropriate under section 401 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 341). Section 401 provides for the promulgation of food standards that "promote honesty and fair dealing in the interest of consumers."

As originally promulgated in 1966 (see 31 FR 1066; Jan. 27, 1966), the provisions of the standard of identity for soda water that relate to caffeine were based apparently on the assumptions that (1) consumers expect "cola" and "pepper" beverages to contain kola nut extract and its naturally occurring caffeine, and (2) the naturally occurring caffeine is, in some undefined sense, a characterizing ingredient of such beverages. As long as these assumptions are valid, it would be appropriate under section 401 of the act to make caffeine a mandatory ingredient in these beverages. It was not clear in 1966, however, nor is it clear now, precisely how caffeine (as opposed to the kola nut flavoring extract in which caffeine naturally occurs) actually affects the characteristics of "cola" and "pepper" soda waters, if at all.

In recent years, consumers have questioned whether it is appropriate to require "caffeine from kola nut extract and/or other natural caffeine-containing extracts" as a mandatory ingredient in "cola" and "pepper" soda waters. In 1974, Consumers Union argued that requiring caffeine in these beverages is contrary to the public health and that manufacturers should be free to produce, and consumers free to choose, decaffeinated cola and pepper drinks (Ref. 1). (See 40 FR 26266; June 23, 1975). In 1979, the Federation of Homemakers petitioned FDA on safety grounds to prohibit the use of added caffeine in all soda water beverages and to allow caffeine in "cola" and "pepper" beverages only in "trace amounts" as a natural constituent of kola nut extract or other caffeine-containing extracts (Ref. 2).

FDA has reevaluated the standard of identity for soda water and, for the reasons discussed below, the agency is proposing to amend the standard to delete the requirement that "cola" and "pepper" beverages contain "caffeine from kola nut extract and/or other natural caffeine-containing extracts." As amended, the standard would designate kola nut extract per se as the mandatory, characterizing ingredient in "cola" and "pepper" beverages and allow explicitly for these beverages to be decaffeinated. The amended standard would continue to allow the use of naturally occurring and added caffeine as optional ingredients up to a maximum total level of 0.02 percent by weight.

The primary reason for FDA's proposal is that there appears to be little or no basis for regarding caffeine per se to be a characterizing ingredient of "cola" or "pepper" beverages. First, as currently written, the standard sets no minimum level at which caffeine must be present and thus already allows the production of "cola" and "pepper" beverages that are virtually (though not completely) free of caffeine. FDA is unaware of evidence demonstrating that the minute amounts of caffeine necessary to satisfy the current standard have any functional or other characterizing effect in the beverages.

Second, at least one manufacturer, the Royal Crown Bottling Co., is marketing with apparent success a "cola" beverage that is claimed to be caffeine-free. This product, called RC-100, is not subject to the standard of identity for soda waters because it is artificially sweetened (see 21 CFR 165.175(a)) and thus a food for special dietary use (see 21 CFR 105.3(a)(2)). Nevertheless, the fact that a manufacturer can gain consumer acceptance of a "caffeine-free" cola belies the notion that consumers expect colas to contain caffeine.

Third, to an increasing extent, soda water beverages other than "cola" and "pepper" beverages contain caffeine as an optional ingredient in amounts equal to or greater than the amount of caffeine ordinarily present in the natural extract used in flavor "cola" and "pepper" beverages (Ref. 3). This fact makes it increasingly difficult to conclude that caffeine characterizes "cola" or "pepper" beverages, any more than it characterizes other soda water beverages to which it is added.

In the absence of convincing evidence that caffeine per se, rather than the kola nut extract in which it naturally occurs, is a characterizing and thus necessary ingredient of "cola" and "pepper" beverages, FDA believes it is appropriate under the standard established in section 401 of the act for promulgating food standards to allow consumers maximum opportunity to choose whether the "cola" and "pepper" beverages they buy should contain caffeine.

Individual consumers may wish to avoid caffeine for any number of personal reasons. By amending the soda water standard to provide for decaffeinated "cola" and "pepper"

beverages, as proposed here, FDA would leave to consumers the decision on whether to purchase decaffeinated "cola" and "pepper" drinks.

FDA is proposing to allow the continued use of caffeine as an ingredient in soda water beverages, but that use of caffeine, as well as other food uses, may be affected in the future by the ultimate outcome of FDA's evaluation of caffeine's safety, referred to above. The changes FDA is proposing to make in the standard of identity for soda water are not intended to imply that FDA has made any final judgments about caffeine's safety, or lack of it. Those judgments will be made through the process initiated elsewhere in this issue of the **Federal Register** in which FDA has raised some questions about the safety of caffeine and has proposed to require the performance of additional studies needed to resolve the questions. If FDA should conclude that caffeine can no longer be used safely in soda water, it will, of course, take appropriate action to amend the standard of identity acordingly. If, on the other hand, caffeine's safety is affirmed, the changes FDA has proposed in the standard of identity would still be justified for the reasons discussed in this document.

In addition to any other aspect of this proposal on which interested persons wish to comment, FDA specifically solicits comments on the following questions:

1. Are any natural flavoring extracts other than kola nut extract used in making "cola" or "pepper" beverages? FDA knows of none and thus is proposing in the amended standard to designate only kola nut extract as the mandatory ingredient.

2. What processes are used, or may be used, in decaffeinating natural caffeine-containing extracts? What degree of decaffeination (in percentage terms) is achieved by each of these processes?

3. What additional nomenclature should be allowed, or required, to describe "cola" or "pepper" beverages that contain no added caffeine and have been made from decaffeinated kola nut extract? What degree of decaffeination should trigger the use of any additional nomenclature?

FDA periodically announces by notice in the **Federal Register** mandatory uniform effective dates for compliance with food labeling requirements. The current mandatory uniform effective date is July 1, 1981 (43 FR 44830; Sept. 29, 1978). The agency proposes that any final regulation based upon this proposal become effective in accordance with a new mandatory uniform effective date for compliance with food labeling requirements to be announced in a future **Federal Register** notice, but not sooner than 1 year after publication in the **Federal Register** of any final regulation based upon this proposal.

The agency has determined under 21 CFR 25.24(b)(13) (proposed December 11, 1979; 44 FR 71742), that this proposed action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

References

1. Letter from Marsha B. Cohen, Attorney, Washington Office, Consumers Union, to Hearing Clerk, Food and Drug Administration, dated July 23, 1974.

2. Citizen petition submitted to Hearing Clerk, FDA, by the Federation of Homemakers (Docket No. 79P-0344/CP), dated August 30, 1979.

3. Letters (with attachments) from Dr. Howard R. Roberts, National Soft Drink Association, to Mr. Robert W. Moore, Bureau of Foods, FDA, dated September 18 and 20, 1979.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 401, 701(e), 52 Stat. 1046 as amended, 70 Stat. 919 as amended (21 U.S.C. 341, 371(e))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Part 165 be amended by revising § 165.175 to read as follows:

§ 165.175 Soda water.

a. *Description.* Soda water is the class of beverages made by absorbing carbon dioxide in potable water. The amount of carbon dioxide used is not less than that which will be absorbed by the beverage at a pressure of one atmosphere and at a temperature of 60° F. It either contains no alcohol or only such alcohol, not in excess of 0.5 percent by weight of the finished beverage, as is contributed by the flavoring ingredient used. Soda water designed by any name which includes the word "cola" or "pepper" shall contain Kola nut extract, which may be decaffeinated. Caffeine may also be added to any soda water. The total caffeine content in the finished food shall not exceed 0.02 percent by weight. Soda water may contain any safe and suitable optional ingredient, except that vitamins, minerals, and proteins added for nutritional purposes and artificial sweeteners are not suitable for food encompassed by this standard.

(b) *Nomenclature.* (1) The name of the beverage for which a definition and standard of identity is established by this section, which is neither flavored nor sweetened, is soda water, club soda, or plain soda.

(2) The name of each beverage containing flavoring and sweetening ingredients shall appear as "soda" or "water," or "carbonated beverage," the blank to contain the word or words that designate the characterizing flavor of the soda water as prescribed in § 101.22 of this chapter.

(3) If the soda water is one generally designated by a particular common name, for example, ginger ale, rootbeer, or sparkling water, that name may be used in lieu of the name prescribed in paragraph (b)(1) and (2) of this section. For the purpose of this section, a proprietary name that is commonly used by the public as the designation of a particular kind of soda water may be used in lieu of the name prescribed in paragraph (b)(1) and (2) of this section.

(c) *Label declaration.* Each of the optional ingredients used shall be declared on the label as required by the applicable sections of Part 101 of this chapter.

Interested persons may, on or before December 22, 1980, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the above office betwee 9 a.m and 4 p.m., Monday through Friday.

Executive Order 12044 does not apply to regulations issued in accordance with the formal rulemaking provisions of the Administrative Procedure Act (5 U.S.C. 556, 557). Food standards promulgated under 21 U.S.C. 341 and 371(e) fall under this exemption.

Dated: October 16, 1980.

Mark Novitch,

Acting Commissioner of Food and Drugs.

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21 CFR Parts 180 and 182

[Docket No. 80N-0418]

Caffeine; Deletion of GRAS Status, Proposed Declaration That No Prior Sanction Exists, and Use on an Interim Basis Pending Additional Study

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: The Food and Drug administration (FDA) is proposing to

delete caffeine used as an added food ingredient from the list of substances that are generally recognized as safe (GRAS), to declare that no prior sanction exists for the use of caffeine as an added food ingredient, to restrict the use of caffeine as an added food ingredient to current uses and levels, and to require that the presence of caffeine as an added ingredient be reflected on the product label in the ingredient declaration. Under this proposal, the current uses of added caffeine would be permitted under an interim food additive regulation pending the completion of studies that are considered necessary to resolve questions about the safety of caffeine added to food. These questions include the potential fetotoxic and teratogenic properties of caffeine, the comparative metabolism and pharmacokinetic handling of caffeine in humans and experimental animals, the potential behavioral affects of caffeine, particularly in children, the potential reproductive effects of caffeine, and the potential carcinogenicity of caffeine. The studies FDA proposes to require include both animal studies and human epidemiological studies. In addition, there are questions that need to be addressed about the purpose for which caffeine is added to foods, especially soft drinks. This proposal does not directly affect the caffeine that occurs naturally in such foods as coffee and tea. In a related proposal published elsewhere in this issue of the **Federal Register**, FDA is proposing to amend the soda water standard to allow for decaffeinated cola- and pepper-type soda waters.

DATE: Comments must be received on or before December 22, 1980.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's office) (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Corbin I. Miles, Bureau of Foods (HFF–335), Food and Drug Administration, 200 C St. SW, Washington, DC 20204, 202–472–4750.

SUPPLEMENTAL INFORMATION:

I. Introduction

Caffeine has been a widely consumed constitutent of the food supply for many years, both as a naturally occurring constituent of such foods as coffee, tea, and chocolate and as an added ingredient in a variety of foods and beverages, most prominently cola-type soft drinks. Despite caffeine's well-known stimulant properties, its use as an added ingredient in soft drinks and other foods has been regarded by the food industry to be generally recognized as safe (GRAS); and FDA's regulations formally list added caffeine as a GRAS ingredient in cola-type soft drinks. The GRAS status of caffeine has exempted it over the years from the food additive sections of the law and their requirement that its safety be proven to FDA by a sponsor. As part of its program to review the safety of all substances listed in its regulations as GRAS, FDA has reviewed the safety of caffeine and has identified several questions about its safety that need to be addressed. Based on these questions, FDA proposes that the use of caffeine as an added ingredient in food should no longer be considered GRAS and that a variety of scientific studies be conducted to address the safety questions. In addition, there are questions about the purpose for which caffeine is added to food, especially soft drinks, that need to be addressed.

After a background discussion on the GRAS review program and the current legal status of caffeine, this document presents the data on caffeine that raise safety questions, explains the basis for FDA's proposal to remove added caffeine from the GRAS list, and describes the studies FDA considers necessary to resolve the existing questions about caffeine's safety and function as an added food ingredient.

II. Background

A. The GRAS Review

Since 1970, FDA has been conducting a comprehensive review of the safety of those human food ingredients that are currently listed in FDA regulations as either generally recognized as safe (GRAS) (21 CFR Part 182) or subject to a prior sanction (21 CFR Part 181). This ongoing review program, commonly referred to as the "GRAS review," has resulted to date in the initiation by FDA of approximately 65 rulemaking proceedings in which the agency has proposed either to affirm the GRAS status of the substance under review (see 21 CFR Part 184) or, where appropriate, to take action to restrict or prohibit use of the substance. The actions proposed in this document with respect to caffeine are, in part, a product of the GRAS review program.

The GRAS and "prior-sanctioned" categories of food substances were established by Congress in 1958 when it enacted the Food Additives Amendment of 1958 (Pub. L. 85–929, 72 Stat. 1784–1789). In that amendment to the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 et seq.), Congress defined the term "food additive," in section 201(s) of the act (21 U.S.C. 321(s)), as follows:

> (s) The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include—
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> * * * * *
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> (4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this Act, the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat. 1260), as amended and extended (21 U.S.C. 71 and the following); . . .
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> * * * * *

Under this definition of "food additive," substances that are GRAS, or that are subject to a prior sanction as defined in section 201(s)(4) of the act, are not food additives and, thus, are not subject to the premarketing safety review made applicable to food additives by the Food Additives Amendment (see section 409 of the act, (21 U.S.C. 348)). Prior-sanctioned substances remain subject, however, to the general adulteration provisions in section 402 of the act, 21 U.S.C. 342, which prohibit the use of added substances that "may render [the food] injurious."

In order to clarify the food additive status of many substances that were being used in food at the time the Food Additives Amendment was enacted, and thus facilitate implementation of the new provisions requiring premarket approval of food additives, FDA established lists of substances that the agency considered to be GRAS (21 CFR Part 182) or subject to a prior sanction (21 CFR Part 181). The regulations establishing the original, partial lists of GRAS and prior-sanctioned substances became final in 1959 (see 24 FR 9368; Nov. 20, 1959) and 1960 (see 25 FR 866; Feb. 2, 1960), respectively. The law, however, did not then, nor does it now, preclude manufacturers from making their own decisions concerning the GRAS status of ingredients prior to marketing them. If FDA disagrees with a

manufacturer's determination that a substance is GRAS (and thus eligible for marketing without the FDA safety review and approval required for food additives), it is FDA's legal burden to take the appropriate steps to end its use as a GRAS substance.

FDA's decisions to place substances on the original GRAS lists were based on the data available at the time the lists were established and on the then current state of knowledge in the field of toxicology. Likewise, the pre-1958 approvals by FDA and the U.S. Department of Agriculture that qualified substances for prior-sanctioned status reflected the best safety judgments that could be made at the time based on existing knowledge. During the ensuing years, however, as more data became available on the properties of particular substances and as the science of toxicology developed, it became apparent that, in order to ensure the safety of the food supply, the agency's earlier safety determinations should be reviewed and modified where appropriate. To this end, FDA initiated the GRAS review program in 1970.

To carry out the GRAS review, FDA conducted surveys of food manufacturers and searched the scientific literature to collect current data on the levels of consumption and the toxicity of substances that are listed as GRAS or subject to a prior sanction. Under a contract with FDA, the Federation of American Societies for Experimental Biology (FASEB), acting through its Select Committee on GRAS Substances (SCOGS), compiled and evaluated the data and made recommendations to the agency concerning the appropriate action to take with respect to each substance under review. In preparing its recommendations on particular substances, FASEB held public hearings to provide an opportunity for interested persons to submit additional information and to express their views about the proper regulatory status of the substance under review. A detailed discussion of the role FASEB plays in the GRAS review is provided in *Federation Proceedings*, Vol. 36, No. 11 (October 1977) (Ref. 1).

FDA reviews FASEB's evaluation of the data and its recommendations and considers any additional information not available to FASEB. The agency then makes its own determination concerning the GRAS status of the substance. The procedures and the substantive criteria FDA applies in determining and affirming the GRAS status of food ingredients are set forth in §§ 170.30, 170.35, 184.1, and 186.1 (21 CFR 170.30, 170.35, 184.1, and 186.1). (The substantive criteria will be discussed below as they apply to the use of added caffeine.)

If FDA concludes that the substance under review is GRAS, it proposes to delete the substance from the original GRAS list in Part 182 (21 CFR Part 182) and proposes a regulation for inclusion in Part 184 (21 CFR Part 184) or Part 186 (21 CFR Part 186) affirming the substance's GRAS status and specifying the conditions of use for which the substance is considered GRAS. If FDA concludes that a substance can no longer be considered GRAS, the agency's usual course of acton is to propose to delete the substance from the GRAS list and to declare that the substance is a food additive that cannot be used in food unless approved as a food additive under section 409 of the act (21 U.S.C. 348).

There is, however, an intermediate step the agency can take, under appropriate circumstances, when it decides that a substance can no longer be considered GRAS. Under Part 180 of its regulations (21 CFR Part 180), FDA can permit the use of such a substance on an interim basis, notwithstanding the safety question(s) that preclude affirming GRAS status, if the agency finds that "* * * there is a reasonable certainty that the substance is not harmful and that no harm to the public health will result from the continued use of the substance for a limited period of time while the question raised is being resolved by further study." (21 CFR 180.1(a)). Substances approved on this basis are referred to as "interim food additives." Under Part 180, FDA can condition the continued use of an interim food additive upon a commitment by interested persons to conduct the studies necessary to resolve questions about the safety or functionality of the substance.

As part of the rulemaking process FDA uses to implement the conclusions reached in the GRAS review process, FDA routinely determines whether a prior sanction exists for the substance under review. If a prior sanction for a particular use is found to exist, then, of course, the substance is exempt from regulation as a food additive, on an interim basis or otherwise.

B. Caffeine

1. *Uses and resulting human exposure.* Caffeine is a member of a class of nitrogen-containing substances known as alkaloids. Its chemical name is 1,3,7-trimethylxanthine, and its empirical formula is $C_8H_{10}N_4O_2$. In the pure state, caffeine is a white powder or a mass of glistening, white needles. Food grade caffeine is listed in the Food Chemicals Codex (2d ed., 1972) (Ref. 2) and its First Supplement (Ref. 3) as containing not less than 98.5 percent $C_8H_{10}N_4O_2$, calculated on the anhydrous basis. The limits established in the Food Chemicals Codex for impurities in food grade caffeine are arsenic (as As), not more than 3 parts per million (ppm); heavy metals, not more than 20 ppm; and lead, not more than 10 ppm. Food grade caffeine should also pass a specified test for the presence of other alkaloids.

Caffeine occurs naturally, but it can also be made synthetically. In nature, it is present at up to 1.5 percent in seeds of coffee (*Coffea arabica* L.) and up to 5 percent in the leaves of tea (*Camellia sinensis*). Caffeine is also a natural component of chocolate (*Theobroma cacao* L.) and the kola nut (*Cola acuminata* Schott and Endl. and related species). Caffeine frequently occurs in nature in association with other chemical substances related to it, such as theobromine and theophylline. Caffeine can be prepared for commercial use by extraction from coffee or tea wastes, by partial synthesis from theobromine, or by total synthesis from various starting materials. One synthetic method uses urea and chloroacetic acid as starting materials, and another uses dimethyl carbamide and malonic acid. According to the Encyclopedia of Food Technology, the primary source of the caffeine that is used as an added ingredient in food is methylation of theobromine obtained from cocoa wastes. A secondary source is solvent or water extraction from coffee beans or tea leaf waste (Ref. 4).

Caffeine is a pharmacologically active substance that is used in a number of prescription and over-the-counter drugs. The major pharmacological effect of caffeine is on the central nervous system, but it can also stimulate the heart and increase cardiac output. Caffeine with sodium benzoate is given by physicians subcutaneously or intramuscularly in dosages of 0.5 to 1.0 grams as a central nervous system stimulant. In addition to its use in prescription drugs, caffeine is the active ingredient in many over-the-counter drugs used to maintain wakefulness. The dosage level in these over-the-counter (OTC) stimulants is usually 100 mg or 200 mg per tablet. Caffeine also is used in a variety of OTC analgesic, diuretic, cold, and diet-aid preparations at single dose levels ranging from approximately 30 to 200 mg.

Caffeine is used on a limited basis as an added ingredient in several categories of nonbeverage foods, including baked goods, frozen dairy

desserts, gelatin puddings and fillings, and soft candy, reportedly as a flavoring agent. The overwhelmingly predominant use of caffeine as an added ingredient in food, however, is in soda water beverages ("soft drinks"); and most of that use (approximately 80–90 percent) is in cola-type soft drinks (Ref. 5). FDA believes that the soft drink use of caffeine accounts for the vast majority of the estimated 2 million pounds of caffeine added to food annually in the United States. (This 2 million pounds does not include the caffeine that occurs naturally in coffee, tea, etc.) Under the current version of FDA's standard of identity for soda water beverages (21 CFR 165.175), caffeine from kola nut extract and/or other natural caffeine-containing extracts is a mandatory ingredient in "cola" or "pepper" type soda water beverages, and additional caffeine from any source, natural or synthetic, may be used as an optional ingredient in any soda water beverage (up to 0.02 percent of the finished food).

In its report to FDA on caffeine (Ref. 6), FASEB presented data concerning the levels of exposure to caffeine experienced by consumers of soft drinks. Using survey data on the frequency of consumption of these beverages among various age groups and the average serving size, and assuming a caffeine level in the beverage of 0.01 percent, FASEB reported the mean consumption of caffeine from soft drinks, among those who consume them, to be 0.17 mg/kg body weight/day in the 0 to 11 month age group; 0.49 mg/kg/day in the 1 to 5 year age group; 0.31 mg/kg/day in 6 to 11 year age group; 0.21 mg/kg/day in the 12 to 17 year age group; and 0.18 mg/kg/day in the 18 and older age group (Table III, Ref. 6). Among the heaviest consumers of soft drinks (those in the 90th to 100th percentile), FASEB found the exposure levels to be significantly higher: 1.8 mg/kg/day in the 1 to 5 year age group; 1.1 mg/kg/day in the 6 to 11 year age group; 0.71 mg/kg/day in the 12 to 17 year age group; and 0.66 mg/kg/day in the 18 and older age group (Table IV, Ref. 6). It is noteworthy that the highest exposure to caffeine from soft drinks on a mg/kg/day basis is among young children, especially those in the 1 to 5 year age group. FDA considers the FASEB data to provide reasonable estimates of the levels of human exposure to caffeine from soft drinks.

FASEB also presented data comparing the levels of caffeine exposure from soft drinks with levels of caffeine exposure from all food sources, including coffee, tea, chocolate, etc. (Ref. 6). These data show that the proportion of total caffeine exposure from soft drinks varies both among the age groups and between average and heavy consumers of soft drinks. For example, persons in the 18 and older category who consume an average amount of soft drinks get the smallest proportion of their total dietary exposure to caffeine from soft drinks: 0.18 mg/kg/day of their total 2.4 mg/kg/day exposure (or 7.5 percent) is from soft drinks (Table III, Ref. 6). On the other extreme, children in the age category of 1 to 5 years who are in the 90th to 100th percentile of consumption of soft drinks get 1.8 mg/kg/day of their total 3.0 mg/kg/day exposure (or 60 percent) from soft drinks (Table IV, Ref. 6). Limited data exist concerning exposure to caffeine among pregnant women. Based on data collected by the Market Research Corporation of America, the mean consumption of caffeine among pregnant women from coffee alone is estimated to be approximately 2.9 mg/kg/day (Ref. 7).

2. *Regulatory status of caffeine as a food ingredient.* Caffeine is one of the substances FDA included on the original GRAS list following enactment of the Food Additives Amendment of 1958 (see 26 FR 938; Jan. 31, 1961). FDA listed caffeine as GRAS for use as a multiple purpose ingredient in cola-type beverages at a level not to exceed 0.02 percent of the beverage (21 CFR 182.1180). The only other formal FDA recognition of caffeine as a human food ingredient is in the standard of identity for soda water (21 CFR 165.175), where, as mentioned above, "caffeine from kola nut extract and/or other natural caffeine-containing extracts" is included as a mandatory ingredient in all "cola"- and "pepper"-type soda water beverages. Caffeine from other sources is also permitted as an optional ingredient in all soda water beverages, at a level not to exceed 0.02 percent.

The Flavor Extract Manufacturers' Association (FEMA) lists caffeine among the substances it considers to be GRAS for general use as a flavor substance (Ref. 8).

Until now, FDA has not taken issue with the FEMA determination; and it is on the basis of its presumed GRAS status as a general use flavor substance that caffeine is currently being used on a limited basis as a flavoring agent in the nonbeverage food categories mentioned above.

As noted above, FDA heretofore has allowed the addition of caffeine to foods and beverages based on its GRAS status. Since FDA proposes in this rulemaking to declare added caffeine no longer GRAS and to regulate added caffeine as an interim food additive under section 409 of the act, the agency must resolve whether any uses of added caffeine are the subject of a prior sanction as defined in section 201(s)(4) of the act. As explained earlier, any use of caffeine that has a prior sanction is excluded from the definition of the term "food additive" and thus cannot legally be included in the interim food additive regulation FDA is proposing to adopt. Such uses would remain lawful, subject only to the general adulteration provisions of the act (see section 402(a)(1) of the act (21 U.S.C. 342)).

Although FDA was aware of the use of caffeine in cola-type soft drinks prior to enactment of the Food Additives Amendment in 1958 and, after 1911, took no regulatory action against that use, the agency does not believe that it explicitly approved that, or any other, food use of added caffeine prior to September 6, 1958. In preparing this proposal, FDA searched its files for documents that relate to the question of whether it granted a prior sanction for caffeine in food (Ref. 9). Several documents, including a March 7, 1940 FD&C Act Trade Correspondence (TC/144), support FDA's tentative conclusion that no prior sanction exists because they discourage the use of caffeine as a food ingredient. Other pre-1958 documents are more equivocal about caffeine, acknowledging its long-time use in cola beverages or stating that there is no scientific evidence that caffeine is hazardous to health as ordinarily consumed in cola drinks.

As a part of this rulemaking proceeding, FDA specifically solicits the submission of comments on the several documents discussed above (Ref. 9) as well as any other evidence relating to whether a prior sanction exists for any uses of added caffeine in food. At this time, FDA proposes to declare that no prior sanction exists for any specific use of added caffeine in food, because FDA has no evidence of the explicit approval of added caffeine that is necessary to constitute a prior sanction (see 21 CFR Part 181).

Persons who intend to assert or rely on a prior sanction for added caffeine must submit proof of its existence in response to this proposal. Under § 181.5(d) (21 CFR 181.5(d)), FDA will consider the failure of any person to come forward with proof of an applicable prior sanction in response to this proposal to constitute a waiver of the right to assert or rely on such prior sanction at any time. If, however, FDA receives acceptable new evidence of a prior sanction, or convincing comments on the documents identified above, it will modify the proposed interim food additive regulation to exclude the prior-

sanctioned use from coverage by the regulation and propose a rule to recognize the prior sanction or sanctions.

The presence of caffeine in food as an added food ingredient (as in cola-type beverages and certain other, nonbeverage foods) is to be distinguished for purposes of this document from the presence of naturally occurring caffeine in such foods as coffee, tea, and chocolate. Although the consumption of foods containing naturally occurring caffeine is widespread and, as discussed above, very significant in terms of overall human exposure to caffeine, this document deals only with the regulatory status of the added uses of caffeine. Limiting the scope of this document to added caffeine is appropriate for a number of legal and practical reasons, which are discussed in a later section of this document.

III. FASEB Report on Caffeine

Consistent with the purpose of the GRAS review program, the task assigned to FASEB by FDA was to review the existing data on caffeine and make a recommendation to FDA on whether caffeine as an added ingredient in cola-type beverages should remain on FDA's list of GRAS substances (see 21 CFR 182.1180). As noted earlier, that use of caffeine is the only one listed in FDA's GRAS regulations.

FASEB submitted its report on caffeine to FDA in May 1978. Relying on a scientific literature review on caffeine prepared under FDA's sponsorship, as well as other sources, the FASEB report summarized the available data on caffeine consumption and on the biological properties of caffeine, including data on caffeine's toxicity. Copies of the scientific literature review and the FASEB report are on file with the FDA Hearing Clerk (HFA–305), Rm. 4–65, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 (Refs. 10 and 6, respectively). Copies may be purchased from the National Technical Information Service (NTIS), 5285 Port Royal Rd., Springfield, VA 22161. The NTIS Order No. for the literature review is PB–234–894/AS; the price code is A16. For the FASEB report on caffeine, the NTIS Order No. is PB–283–441/AS, and the price code is A05.

In the opinion section of its report (Section V, Ref. 6), FASEB referred to the existing data concerning the potential mutagenicity, teratogenicity, and carcinogenicity of caffeine, as well as the data concerning other possible effects of long-term exposure to caffeine. FASEB noted that in some animal test systems, generally involving very high dosage levels, some adverse effects of these kinds have been associated with exposure to caffeine. FASEB concluded, however, that the available data concerning these effects do not demonstrate a risk to humans from exposure to caffeine as currently used in soft drinks (which the FASEB report referred to collectively as "cola-type beverages").

In explaining its ultimate conclusion that caffeine in "cola-type beverages" should no longer be considered GRAS, FASEB placed primary emphasis on the potential behavioral effects of caffeine in children. FASEB pointed out that the concerns about the behavioral effects of caffeine are less for adults "* * * than for children where there can be chronic consumption of caffeine in cola-type beverages during the period of brain growth and development. It is during this period of plasticity that the developing central nervous system is most sensitive to the effects of all aspects of the environment. The estimated levels of caffeine intake at these ages are near those levels that are known to cause central nervous system effects in adults."

Although it acknowledged that the available data are not adequate to answer the question of whether chronic exposure to caffeine in "cola-type beverages" poses a potential hazard to children and others, FASEB stated that it "* * * views with concern the continued addition of caffeine to cola-type beverages, representing as it does a unique addition to food of a pharmacologically active central nervous system stimulant." FASEB said: "* * * there is a possibility that behavioral effects in children from infancy through adolescence exist, even though these potential effects are neither adequately documented nor are their consequences clear." FASEB said further that: "A series of rigorously controlled chronic studies in appropriate species, including fetal, neonatal, and growing animals, of the immediate and ultimate behavioral and cardiovascular effects of caffeine added to the diet and given in cola-type beverages, would reduce areas of speculation."

FASEB then stated its formal conclusions as follows:

A. While no evidence in the available information on caffeine demonstrates a hazard to the public when it is used in cola-type beverages at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies be conducted.

B. It is inappropriate to include caffeine among the substances generally recognized as safe (GRAS). At current levels of consumption of cola-type beverages, the dose of caffeine can approximate that known to induce such pharmacological effects as central nervous system stimulation.

One member of the FASEB committee that considered caffeine filed a minority report. That report will be discussed in a later section of this document.

IV. FDA's concerns About Added Caffeine

A. Introductions

FDA has carefully considered the data on caffeine discussed in the FASEB report, as well as additional data not available to FASEB at the time it prepared its report. FDA shares FASEB's concern about the addition to food of a pharmacologically active agent, including FASEB's uncertainty about the potential behavioral effects of caffeine, especially in young children. FDA also is proposing to adopt FASEB's basic conclusion that, due to questions about the safety of caffeine, it is no longer appropriate to continue the listing of added caffeine as a GRAS substance.

However, due to recently developed evidence concerning the capacity of caffeine to cause birth defects in rats, FDA's primary concern about caffeine has shifted from caffeine's potential behavioral effects to its potential teratogenicity. As explained below, much uncertainty still exists about whether caffeine actually increases the risk of birth defects in humans, but the data now available from animal studies are significant enough to be of serious concern and to justify additional research directed toward resolving as soon as possible the uncertainties about caffeine's potential teratogenicity in humans.

In addition, due for the most part to a lack of the data normally required to support the safety of a food additive rather than affirmative evidence demonstrating a potential health risk FDA is proposing to require studies addressing the capacity of caffeine to cause adverse behavorial effects, reproductive effects, and cancer. These additional studies, coupled with the studies on caffeine's potential teratogenicity, should resolve the question of caffeine's safety as a human food ingredient. Finally, FDA proposes to resolve the question of caffeine's functionality as an added ingredient in food by requiring manufacturers to identify the purpose or purposes for which caffeine is used and demonstrate that the amounts used are necessary and effective for the intended purpose(s).

The following subsections of this document present the data and information that support FDA's proposal to remove added caffeine from the

GRAS list and that justify the studies FDA is proposing to require.

B. Teratology

1. *Animal data prior to 1979.* In 1979, FDA published a review of the reproduction and teratology studies on caffeine completed and available as of that time (Ref. 11). That review cited a number of investigations, utilizing different methods of dosing and various species and strains of animals, which have indicated that caffeine may have fetotoxic and teratogenic potential.

For example, caffeine injected intraperitoneally into pregnant mice at dose levels of 200–250 mg/kg was embryotoxic and affected palate and limb development of the fetuses (Refs. 12, 13, 14, 15). A single subcutaneous injection of mice with 200 mg/kg caffeine produced cleft palate, micrognathia, hematoma, clubfoot, and digital defects in mice (Ref. 15). Mice given a single subcutaneous injection of 300 or 400 mg/kg had offspring that exhibited digital deformities, shortened extremities, muscular development disorders, cleft palate, facial deformities, and tail and spinal column curvative (Ref. 16). Oral administration of caffeine at 50 mg/kg by intubation produced skull and facial deformities and cleft palates (Ref. 17) and digital deformities (Ref. 18), but no ectrodactyly (partly or completely missing digits) in Swiss mice (Ref. 19); 75 mg/kg caused facial deformities, anophthalmia (missing eyes), and exencephaly (Ref. 20).

Dosing of rats by intubations of caffeine gave evidence of toxicity but produced variable teratogenic responses. At 0.2 to 22.5 mg/kg, no dose-related effects were seen (Ref. 21); 30 mg/kg resulted in decreased litter size and delayed bone ossification in the offspring (Ref. 22). Offspring of rats given 125 to 150 mg/kg showed missing digits and phalanges (Refs. 18, 19); 130 mg/kg caused cleft palates (Ref. 23), and 180 mg/kg caused toxicity and cleft palates (Ref. 23) and abnormalities of an unspecified type (Ref. 24), while 240 mg/kg reportedly was lethal to the fetus (Ref. 23).

Hamsters administered with up to 30 mg/kg caffeine by intubation at days 6 to 10 of gestation showed no frank terata (Ref. 21), but rabbits dosed with 100 mg/kg caffeine exhibited ectrodactyly (Ref. 19).

Caffeine given to rats daily in tap water at 30 mg/kg produced ossification problems and underdevelopment of kidney pelvis (Ref. 22). However, 40 to 50 mg/kg appeared to have neither teratogenic nor growth-retarding effects on the offspring (Ref. 25). Caffeine given daily to mice in drinking water at up to 39 mg/kg caused no dose-related effects, although at 12 to 18 mg/kg some offspring from treated animals were underweight at weaning, and one complete litter was ectrodactylous (Ref. 26).

Caffeine in coffee at up to 38 mg/kg produced fetotoxic effects in rats, such as delayed ossification of rib and skull bones, kidney pelvis underdevelopment, decreased organ to total body weight ratio of brain, lungs, and liver, and decreased bone density of the humerous (Ref. 22).

Rats fed a dietary level of 120 mg/kg of caffeine showed reduced litter size and birth weight (Ref. 27); dietary levels up to 330 mg/kg caused increases in skeletal defects as well as soft-tissue anomalies (Reg. 28).

The FDA review (Ref. 11) noted that many of the studies had deficiencies (e.g., lack of proper control animals, small number of animals, lack of concurrent control animals, insufficient information on procedures). Moreover, many of them were conducted a decade or more ago when teratology study techniques were less developed. Despite these deficiencies, the animal studies available at the time the review was published, taken together, demonstrate clearly that, at sufficiently high levels of exposure, well above what humans are exposed to in the diet, caffeine can cause birth defects in animals. The studies were not adequate, however, to determine with any confidence a no-effect level for the teratogenic effects of caffeine in animals, i.e., the level of exposure at which no teratogenic effects are observed.

2. *FDA study.* Due to the uncertainties left by the existing animal data, FDA initiated in 1979 two teratology studies of caffeine in laboratory animals using up-to-date teratology test methods. The purpose of the two studies was to confirm whether caffeine is an animal teratogen, and, if it is, to further refine the value of the no-effect level.

Both of FDA's teratology studies of caffeine used Osborne-Mendel rats of the FDA strain. The primary difference between the two studies is in the method by which the caffeine was administered to the animals. In the first study, which is now complete, the caffeine was administered by gavage, i.e., by forced feeding of measured amounts through a stomach tube. The advantage of this method is that it permits delivery to the animal of a precise amount of the test substance. One difficulty with the gavage method of administration is that by delivering the daily dose of the test substance in one large amount, it may not accurately reflect the way humans are exposed to the test substance. In the second study, the results of which are not yet available, the caffeine was administered via drinking water consumed *ad libitum.*

In the FDA gavage study of caffeine, animals were randomly assigned to each of six dose levels: 0, 6, 12, 40, 80 and 125 mg/kg/day. Initially, 61 presumably pregnant animals were assigned to each group to allow for a final minimum of 50 pregnant dams per group. Use of excess numbers of animals to allow for false pregnancies or mating failures is normal practice. Caffeine was administered daily by oral intubation on days 0 through 19 of gestation. Concurrent control animals were administered distilled water by intubation on the same days. Six of the pregnant animals died at the highest dose level. A dose-related decrease was seen in the total maternal weight gain during gestation at all dose levels.

On day 20, the pregnant animals were sacrificed and the fetuses delivered by caesarean section. Observations recorded included the number and position of resorption sites (i.e., places in the uterus where post-implantation death has occurred), the number of fetuses (dead and alive), the number of corpora lutea, and the number of implantation sites. Two litters were totally resorbed at 80 mg/kg dose levels. Significant decreases were observed in fetal weights and crown-rump distances in both makes and females at 80 and 125 mg/kg and 4 litters were resorbed at 125 mg/kg. Other increases in resportion also were observed at the 80 and 125 mg/kg and in female fetal weight and crown-rump distance at 40 mg/kg. Extrodactyly (partially or completely missing digits) was observed only at the 80 and 125 mg/kg dose levels. The highest observed no-effect level for ectrodactyly in this study was 40 mg/kg.

Also seen at the 80 and 125 mg/kg levels were assorted skeletal anomalies including misshapen centra, missing centra, reduced dorsal arch, reduced pubis, missing hind phalanges, reduced metacarpals and reduced metatarsals. In addition, delayed ossification of the sternebrae was seen at all dose levels. No soft-tissue variations appeared to be related to caffeine intake. A manuscript describing the results of this study in full detail (Ref. 29) has been accepted for publication by the *Journal of Environmental Pathology and Toxicology.* Complete copies of the protocols on the FDA caffeine teratology studies are included in the record as Refs. 30 and 31.

The gavage study has been completely analyzed by FDA and reviewed by two groups of teratology experts from

outside the Bureau of Foods. The first group of scientific reviewers consisted of Dr. Joseph F. Holson of the National Center for Toxicological Research and Dr. Richard M. Hoar of Hoffman-LaRoche, Inc. (also President of the Teratology Society). These reviewers concluded that the two FDA teratology studies "were designed and are bing conducted by knowledgeable personnel in a thorough and professional manner. Indeed, the size of the studies makes them more 'robust' than most studies of this nature. We conclude that these studies would be judged acceptable by a peer group for an initial teratological screen." The second group of scientific reviewers consisted of Dr. Carole A. Kimmel of the National Center for Toxicological Research and Dr. K. S. Khera of the Food and Drug Directorate of Canada. These reviewers observed that "discussion * * * and a review of the manuscript describing data from the gavage study, failed to uncover any sources of error in the design or conduct of the study. This is a conventional straightforward teratorlogy study conducted in a controlled manner * * *. Inter-observer bias was controlled since Dr. Welsh alone scored all the fetal skeletons and had no prior knowledge of the dose group to which the fetuses belonged. Uniformity in subjective judgment of the subtle sternebral changes was attempted by following a diagrammatic guide * * *. The collection of food consumption data, the large sample size, the relatively wide range and the number of test doses and the highly qualified scientists involved, are all considered strong points."

The FDA gavage study raises serious concerns about caffeine because it is the first large, well-designed and controlled teratology study on caffeine to show irreversible terata (e.g., missing digits) at levels as low as 80 mg/kg, and other adverse, but probably reversible, effects at levels as low as 6 mg/kg. The levels of caffeine exposure at which these effects occurrred in the rats are not significantly greater than those humans might be exposed to in the food supply. The daily doses of 40 mg/kg (the highest observed no-effect level for ectrodactyly) and 80 mg/kg fed to the rats in the FDA gavage study equate on a body weight basis to the amount of caffeine a human female might consume in approximately 12 and 24 strong cups of coffee, respectively; six mg/kg equates to two cups (Ref. 32). in determining the significance of the FDA gavage study for humans, however, it is necessary to consider whether animal teratology studies in general and rat studies on caffeine in particular are reliable indicators of human risk.

3. *Relevance of animal teratology studies to humans.* A fundamental assumption in the estimation of the human health risks posed by chemicals is the ability to extrapolate animal test results to human response. This assumption is the cornerstone of most of FDA's decisions regarding the safety of substances in the food supply. In accepting this assumption, however, FDA does not assume that responses in animal models reflect exactly what will occur quantitatively or qualitatively in humans. What is assumed is the ability of well-designed animal studies to provde an indication of potential risk to humans. Only after careful analysis of experimental results from multiple species can a degree of confidence be ascribed to the probability that this potential risk will materialize in the human population. If it can be demonstrated scientifically, however, that a result from a particular animal study is not relevant as a predictor of human risk, then that result would not be employed in making safety assessments no matter how drastic the animal results. Ultimately, conclusions regarding the precise risk to humans for any substance can only be arrived at by using appropriate human data.

Animal cancer studies are particularly well-suited to predicting human response. This is true for a number of reasons that have come to be understood from the extremely large body of scientific evidence that has been developed for substances having the ability to induce cancer. For the purpose of this document, however, it is necessary to focus on the problem of extrapolating teratology data from animals to humans.

Interpretation of the relevance of teratology studies to human is affected by many considerations, which combine to make the interpretation of teratology studies complex, difficult, and uncertain (Ref. 33). These considerations, which are the same whenever one attempts to extrapolate from an observed teratologic response in one species to what might be expected to occur in another, include:

1. Physiological and biochemical differences that affect the absorption, metabolism, and excretion of the substance.

2. Variability in placental barriers.

3. Differences in susceptibility to chemical interactions at the cell, tissue, organ, and organ system levels.

4. Variability in background incidence of disease.

5. Variability in the gestational development sequence.

These factors must be taken into account, to the extent the available data permit, when one attempts to assess the relevance to humans of any specific teratology study conducted in a particular species on a particular chemical. They will be discussed below as they relate to the animal studies on caffeine.

In an effort to better understand as a general matter the relevance of animal teratology studies to humans, several investigators have examined the literature to determine the extent to which known or suspected human teratogens have also been found to be teratogenic in animals (Refs. 34, 35, 36). FDA's review of the literature reveals a group of 38 compounds for which there are reports of birth defects in humans associated with intake of these compounds during pregnancy (Refs. 36, 37, 38, 39). Of these compounds, all except one have a positive study in at least one animal test species. Furthermore, over 80 percent of the compounds are positive in multiple species. The one exception is a compound that causes otological deficits in humans that would not normally be discovered in test animals at the time of caesarian sacrifice.

Among the most widely tested individual species, a positive teratologic response to the substances identified as known or suspected human teratogens was exhibited 85 percent of the time in the mouse, 80 percent in the rat, 60 percent in the rabbit, 45 percent in the hamster, and only 30 percent in the monkey. Other species have been used to test only a small number of these substances. Nevertheless, there has been a greater than 80 percent correlation with the positive human data for the dog, pig, cow, and cat.

The correlations between human response and the responses of specific species are not as good for the compounds that do not appear to be human teratogens. Of the 165 compounds for which human teratologic effects have not been reported, 28 percent appeared negative in all animal species tested and 50 percent appeared negative in multiple species. However, 41 percent of these 165 compounds appeared to be positive in more than a single animal species. For the most commonly tested species, a non-positive response to the substances for which human teratologic effects have not been reported was observed 80 percent of the time for the monkey, 70 percent for the rabbit, but only 50 percent for the rat, 35 percent for the mouse, and 35 percent for the hamster.

Taken together, these correlations between human and animal teratologic

response tend to support the assumption that, as a general matter, positive animal teratology studies are at least suggestive of a positive human response. However, the correlations between the human and animal data on the substances that appear negative in humans suggest the limits that likely exist on the predictive power of positive animal studies. In addition, it must be emphasized that the degree of reliance that can be placed on these correlations to support the assumption that animal studies are relevant to humans is limited by the uncertainties that exist in the human data used to identify the 38 known or suspected human teratogens used in the comparisons. Most of the 38 were identified only from a limited number of adverse reactions reported by physicians. Very few have been the subject of rigorous, large-scale epidemiology studies, which provide the only basis for concluding unequivocally that a substance is a human teratogen. Similarly, the data available on the 165 substances for which teratologic effects have not been reported are not of sufficient quantity and quality to establish conclusively that all 165 are not human teratogens.

As revealed by the data just cited, a factor that complicates the use of animal studies to predict potential teratogenic response in humans is the apparent variability in response to teratogenic agents among animal species. The reasons for the apparent variability and its relevance to the reliability of animal studies for predicting human response are not well understood. It is important to realize, however, that the endpoint that is being measured (teratology) is not a single response. Unlike other toxicities, which have clear expressions (such as death, cancer, tumor, or organ damage), teratologic responses are numerous and varied and result from a continuous series of pathologic alterations during fetal development. Whether or not a particular chemical will induce a teratologic response in the fetus is dependent on a variety of factors and influences (listed above) that change from species to species. The mechanism of action in each species can also vary.

It is known that one major source of variability among species derives from the influence of the maternal organism on the way the fetus is affected by a chemical the mother ingests. The site of a chemical's teratogenic action can be primarily in the embryo, in the maternal organism and only secondarily in the embryo, or in both. Wherever the primary site of action is, however, the maternal organism always exerts some influence in determining the teratogenic or other embryotoxic effect of a substance with which it comes into contact, because it is through the mother that the substance is delivered to the fetus. The route and rate of maternal absorption are the initial determinants of the concentration in the maternal bloodstream, but of equal or greater importance is what happens to a foreign chemical after it gets into the maternal blood. For example, it may be excreted by the kidney, metabolized by the liver, kidney, or other organs, bound to protein, stored in various tissues, or it (and/or its metabolites) may simply remain in the blood plasma at varying concentrations for some period of time. The level of concentration in the blood as well as the lengths of time for which various levels are maintained are important in determining the total dosage that will be available for transfer by the placenta to the embryo or fetus.

In conclusion, it is reasonable to conclude that positive animal teratology studies are at least suggestive of potential human response. Well-conducted animal studies that show teratogenic effects at levels of exposure not substantially greater than humans might experience are sufficient to raise substantial questions about the potential risk to humans. However, at this time, no single test species can be said to predict accurately the true human response to a given chemical. Tests in multiple species may increase the predictive reliability of animal test data, but specific differences between the test species and the human system must be considered in evaluating the relevance of particular tests to humans. It is for the latter reason that FDA has reviewed carefully the available data on the comparative metabolism of caffeine, especially between humans and the rat—the species used in FDA's gavage study.

4. *Comparative metabolism of caffeine.* As the previous section indicates, well-designed animal studies that show positive results in more than one species are at least suggestive of the potential teratogenic response of a given substance in humans. As also noted above, however, there are a number of considerations that may limit the ability of any single animal teratology study to predict the response in humans. One of these considerations is the existence of physiological and biochemical differences between species that may affect the absorption, metabolism, and excretion of a substance. In the specific case of caffeine, there are preliminary indications of significant differences between the metabolism of caffeine in humans and experimental animals, although the entire range of these differences has not been thoroughly established.

The available data indicate that there are both major metabolic and pharmacokinetic differences among various species of experimental animals in which caffeine has been reported to cause teratogenic effects, and between those species and humans. For example, following a single oral dose of caffeine in humans, the major urinary metabolite is 7-methylxanthine (Refs. 40). In the rat and mouse, this metabolite is not detected, the major metabolite being 1,3,7-trimethyluric acid, a minor metabolite in man and the rabbit.

In humans, it is clear that most caffeine is first subject to 3-*N*-demethylation to yield paraxanthine (1,7-dimethylxanthine). About 1 to 2 percent of a given dose of caffeine is recovered in human urine as 4-amino-5-(*N*-methylformylamino)-1,3-dimethyluracil (Ref. 41) Callahan and colleagues have recovered 10 to 30 percent of caffeine administered to various individuals as the acetylated diaminouracil derivative (Ref. 42). This metabolite may be produced from another, as yet unidentified, metabolite.

Several factors may influence the metabolism of caffeine in humans. Smoking, which stimulates the elimination of caffeine (Ref. 43), and pregnancy, which slows the elimination of caffeine (Refs. 44, 45, 46), have yet to be investigated with regard to effects on metabolite pattern. Age is also an important factor in caffeine metabolism. The newborn human, as it develops the capacity to dispose of caffeine, also develops the adult metabolite pattern (Ref. 47).

In rats, caffeine appears to be subject to a wider array of metabolic transformations than in humans. Important reactions include oxidation at the 8-position, demethylation at *N*-1, *N*-3, and *N*-7, and hydrolytic ringclearage to the uracil derivative 4-amino-5-(*N*-methylformylamino)-1,3-dimethyluracil (Refs. 41, 48). The production in the rat of the diaminouracil derivative (30 to 40 percent of recovered metabolites or 18 to 25 percent of administered dose) and 1,3,7-trimethyluric acid (14 percent of recovered metabolites) attests to the differences in metabolic pathways and extent of conjugation of diaminouracil between the rat and human. The differences in extent of conjugation are likely to influence the rate at which the metabolites of caffeine are eliminated from the body.

Perhaps more significant than the difference in caffeine metabolite patterns between the rat and man is the

fact that the rat exhibits an apparently different time profile of caffeine elimination from the plasma compared to humans. Specifically, studies on the pharmacokinetics of caffeine suggest that the rat is more likely to accumulate caffeine in the blood after repeated treatment at dose levels higher than 5 mg/kg than is the mouse, rabbit, or human. Dose-dependent kinetics in the plasma disappearance of caffeine are apparent in the rat, resulting in rapid clearance at the lower doses of 5 to 25 mg/kg. At higher doses, however, somewhere between 25 and 50 mg/kg, the time profiles of caffeine elimination by the rat and human appear to cross-over so that the rat actually appears to eliminate caffeine more slowly than the human. This comparison assumes that caffeine elimination in humans continues at a constant rate up to dose levels that are difficult to achieve experimentally in humans. In practical terms, this would mean that at dose levels on the order of those that caused irreversible terata in the FDA gavage study, the rat would maintain higher blood plasma levels of caffeine for longer periods of time than the human, and thereby increase the level and duration of the fetus' exposure to caffeine, as compared to humans.

Caffeine metabolism and pharmacokinetics also have been investgated to some extent in animals other than the rat. The mouse appears to eliminate caffeine from the plasma faster than humans at all dose levels studied (Refs. 40, 41, 44, 49). The rabbit initiates caffeine metabolism by demethylation at the *N*-3 position as in humans, but it also exhibits a dose dependent rate of caffeine elimination similar to rats (Refs. 40, 41, 44, 49). The subhuman primate *Macaca cynomolgus* initiates caffeine metabolism by demethylation of the *N*-7 position, in contrast to humans (Refs. 41, 44).

In sum, similar doses of caffeine in humans and experimental animals will result in exposure of the maternal animal and the developing fetus not only to widely different levels of caffeine, but also to different kinds and amounts of caffeine metabolites. It is not known to what extent these differences in metabolism and pharmacokinetics relate to the observed teratogenic effects in experimental animals. They do raise serious questions, however, about the ability of the animal studies—particularly in the rat—to predict the response of humans to caffeine.

At this time, there are insufficient data to determine whether caffeine *per se* and/or one of its metabolites is the causative agent for the teratogenic effects observed in experimental animals. In the absence of an answer to that question and more complete information on the comparative metabolism and pharmacokinetic handling of caffeine in human and animals, especially the rat, it is not possible to determine with confidence what, if any, potential risk exists for humans based on the existing animal teratology data on caffeine.

5. *Human teratology data.* FDA has reviewed six human epidemiological studies that deal at least in part with the teratological effects of caffeine (Refs. 50, 51, 52, 53, 54, 55). All of these studies to some degree were directly or incidentally concerned with exposure to caffeine and an increased risk of complications of pregnancy. Unfortunately, most, if not all, of these studies have methodological problems associated with them that make it difficult if not impossible to draw any reasonably valid inferences from the results. In general, these studies are flawed by a failure to control important variables that could alter study results. These variables include adequate measures of exposure (amount and length of time of caffeine consumption), intake of alcohol, smoking habits, age at pregnancy, and level of pre-natal care.

Of the six human studies, four were concerned with the dietary intake of caffeine in coffee, while the remaining two were concerned with caffeine exposure as a result of drug usage.

Nelson and Forfar (1971) (Ref. 50) report the results of a retrospective study to compare the drug consumption during pregnancy of mothers of infants with congenital abnormalities (458) compared to the drug consumption of mothers with normal infants (911). No attempt was made to determine caffeine exposure other than caffeine contained in drugs. The authors report that there was no statistically significant difference in caffeine use between the mothers who had malformed infants and those who had normal infants.

In a prospective study of some 50,000 pregnant women, Heinonen et al. (1977) (Ref. 53) identified 5,773 pregnant females who were exposed to caffeine in drug products that also contained aspirin and phenacetin. The study was not designed to address the exposure of the females to caffeine consumed as a dietary ingredient. Although the authors report an increase in birth defects in infants born to mothers who consumed caffeine with aspirin and phenacetine during pregnancy, the increase was not statistically significant, and the authors report that caffeine itself could not be associated with any of the observed effects.

In a study of the effects of tobacco, coffee, and alcohol on prematurity in pregnancy, Van den Berg (1977) (Ref. 52) found that heavy coffee drinking (seven cups or more per day) occurred in 13 percent of the study population of 8,514 pregnant females, while the incidence of such consumption among mothers of low-birth-weight infants was 21.4 percent. However, among heavy coffee drinkers, there is a large proportion of smokers (65.3 percent), and the author concluded that the coffee effect appears to be explainable by the association with smoking. No significant difference was observed in mortality rates or rates of severe congenital anomalies in the infants of females who consumed seven or more cups of coffee per day compared to those who consumed less than seven cups per day.

Mau and Netter (1974) (Ref. 50) reported the results of a study of 5,200 females who were asked to record their coffee consumption on a recall basis as none, seldom, or frequent. No attempt was made to quantify the amount of coffee consumed by number of cups or type of coffee consumed. Results of the study indicated that coffee consumption as reported was associated with a slight increase in the incidence of low birth weight infants (6.6 percent) compared to controls (4.2 percent). The authors report no significant relationship associating coffee consumption with duration of pregnancy, frequency of abortions, or birth defects.

In a study reported by Streissguth et al. (1980), (Ref. 47), some 1,529 pregnant women were observed for the effects of a variety of substances, including coffee, alcohol and tobacco, on pregnancy outcome. The study was conducted through the use of a questionnaire in which the women were asked to recall their caffeine consumption during pregnancy. Although the authors report an incidence of 4 percent for breech presentations, and an incidence of 4 percent for a previous history of spontaneous abortions and stillbirth, associated with caffeine consumption, other variables such as age of mother were no controlled for. The authors did not ascribe any significance to this finding. In addition, the finding of a history of reproductive loss in previous pregnancies may well be associated with a risk factor unrelated to caffeine exposure and certainly requires additional explanation.

In a study by Borlee, et al. (1978) (Ref. 54), which involved 202 malformed children and 175 controls matched for age, sex, and socioeconomic status, the analysis was conducted on 185 cases and 157 controls; no mention is made of

those study subjects lost to followup. A statistically significant association was observed between cases and controls for a history of coffee drinking by mothers. The difference can be isolated, however, to those who drank over eight or more cups a day. Unfortunately, the statistical procedures are not discussed in the paper so it is difficult to determine their adequacy. However, from the number of paired comparisons presented, it appears that simple tests were used that are not suitable for this analysis in many cases. FDA attempted to utilize the proper statistical methods, but the insufficiency of the data presented in the paper made it impossible to perform the proper statistical analysis. Attempts by FDA to obtain from the authors the additional data needed to properly evaluate the study's results have not been successful to date.

From an epidemiological viewpoint, the study's consideration of a possible interaction with smoking appears incomplete. The investigators considered only the percentage of smoking mothers of malformed children; they did not consider the percentage of smoking mothers of normal children. The analysis considering medications only considers the number of medications, not the type of medications. Obviously, the type may be more important.

In a followup to this paper, published in *Science* (1980) in the form of a letter (Ref. 58), the authors of the study have gone to great lengths to advise caution in interpreting its results, citing the preliminary nature and incompleteness of the data. They feel that the data have been interpreted inappropriately by some who have placed great significance on the results.

As indicated previously, the existing human studies are severely weakened by a variety of methodological problems, which become most apparent when attempts are made to use their results to answer questions that the studies are not specifically designed to address. Attempts to quantify caffeine exposure and to relate such exposure to pregnancy outcome, without controlling for a wide variety of other variables that may represent additional risk factors for adverse pregnancy outcomes, appear to confuse rather than clarify the issues. The Interagency Epidemiologic Working Group on Special Problems in Cancer Epidemiology (IEWG) also reviewed these studies and reached the same conclusions about their adequacy as has the agency (Ref. 7).

In summary, FDA concludes that the available human studies, whether taken as a group or singly, do not conclusively determine the relationship between caffeine consumption and teratological effects.

6. *Conclusion.* The available data on the potential of caffeine to cause birth defects clearly raise substantial questions that need to be resolved by further research, but the data do not provide a sufficient basis to conclude that caffeine actually presents a risk of birth defects in humans. The source of the questions about caffeine's potential teratogenicity is the FDA gavage study in rats, which, when viewed against the background of previous animal data, clearly demonstrates that caffeine is capable of causing irreversible terata and other effects in the fetus of the rat at levels of exposure not substantially greater than human might experience from foods and drugs. However, the additional data concerning differences in the pharmacokinetics and metabolism of caffeine in animals and human raise questions about whether animal studies in general, and rat studies in particular, give a reliable indication of caffeine's potenial risk to humans. These data, coupled with the generally inconclusive results obtained in the available human data, make it premature for FDA to conclude that caffeine actually poses a risk to humans. FDA and other public health agencies have consistently urged pregnant women to be cautious in their consumption during pregnancy of any pharmacologically active substances, and this caution extends to caffeine. There is, however, insufficient evidence to conclude that caffeine will cause birth defects in humans.

C. Reproductive Function

In addition to considering data on the potential teratogenic effects of caffeine, which involve effects on the offspring, FDA has evaluated the available data relating to caffeine's potential effect on the reproductive function itself. Like the teratology data, the reproductive data raise questions that require further study, but they do not demonstrate any actual risk to humans.

1. *Animal and human data.* Several investigators have reported that caffeine has no adverse reproductive effects in animals at dose levels of 30 to 50 mg/kg body weight. Thayer and Kensler (Ref. 26) exposed four generations of male and female mice continuously to caffeine in the drinking water at levels of 4 to 5, 12 to 18, and 25 to 39 mg/kg body weight/day. No consistent, dose-related effects of caffeine on fertility, age at sexual maturity, mean litter size, weight of offspring at weaning, sex ratio, or fetal abnormalities were observed. Bachmann et al. (Ref. 25) tested the influence of chronic exposure to caffeine on the reproductivity of albino rats given a sweetened caffeine-containing beverage as the only liquid in the diet for as long as 3.5 years. The average dose was about 40 to 50 mg/kg/day. Mated at 100 days of age, the pairs were kept until the female produced no offspring for a period of 3 months after the last litter. No evidence of sterility or unusual histological changes in the male testes were observed.

In a two-generation rat study (Ref. 27) at a much higher daily dose level of caffeine (125 mg/kg body weight incorporated in the diet); progressive reduction in litter size was observed; birth weights, postnatal survival, and growth rates through lactation were decreased, but growth and survival subsequent to lactation were not affected.

Friedman et al. (Ref. 57) reported that the feeding of 0.5 percent caffeine (about 500 mg/kg) to immature Osborne-Mendel rats for 3 to 16 months can produce severe testicular atrophy and aspermatogenesis in 85 to 100 percent of the animals. However, it is to be noted that no significant testicular atrophy or dose-related pathological effects were observed in a 2-year study of rats receiving dilutions of freshly brewed coffee as the only source of liquid; doses of caffeine were equivalent to about 54, 32, and 14 mg/kg (Refs. 58 and 59).

Ax et al. (Refs. 60, 61, 62) studied the effects of dietary caffeine on the fertility, embryonic loss, and testes of the domestic fowl. Fertility was not impaired in pullets fed 0.05 percent caffeine (estimated to be about 80 mg/kg/day) but embryonic loses were about 16 percent compared to 5 percent in controls. Percentage fertility of eggs from untreated pullets inseminated with semen from mates fed continuously a diet containing 0.1 percent caffeine was measured. Semen from roosters at the start of caffeine feeding produced 30.8 percent fertile eggs. After 14 days of caffeine feeding, egg fertility was 3.3 percent. Semen output and sperm concentration also were markedly affected: by 25 days semen volume was less than one-half the volume at the start of the study and sperm count was depressed by a factor of more than 100. No semen could be collected from roosters that had received caffeine for 30 days. Removal of dietary caffeine resulted in resumption of semen production and return of egg fertility to normal levels.

A recent report by Palm et al. (Ref. 22) suggests the occurrence of some adverse reproductive effects in rats at oral dose levels of 30 to 38 mg/kg body weight. In this study, groups of 20 pregnant Sprague-Dawley rats were given

approximately 9, 19, or 38 mg/kg/day caffeine (as diluted coffee in drinking water) 5 weeks prior to and during gestation; another group was given 30 mg/kg/day caffeine in the drinking water during pregnancy; and another group was given a similar dose of caffeine by oral intubation. Most pregnant animals were killed on day 19 of gestation and evaluated for teratogenicity, as discussed earlier. In addition, 5 pregnant animals from each treatment group and concurrent controls were allowed to deliver and rear their young. During the nursing period, only the coffee-treated females continued to receive caffeine. Following weaning, the F_1 generation offspring were not treated, but were bred to evaluate their ability to reproduce. The F_2 pups were examined as to gross abnormalities, mean body weight, and post-weaning survival. In the coffee-treated animals sacrificed on day 19, there was a statistically significant decrease in organ to total body weight ratio of fetal brain, lungs, and liver at the 38 mg/kg caffeine level. Fetal liver weights and lung weights were also reduced in the caffeine-gavage and caffeine-drinking water groups, respectively. Malformations were found in both control and treated animals with a small but statistically significant increase in cryptorchidism (failure of the testes to descend into the scrotum) in the groups receiving caffeine. The reproductive performance suggested that the percentage of F_1 females becoming pregnant was less than controls, but not statistically so. However, the mean number of days required to achieve pregnancy was statistically greater for the two high dose coffee groups and for the two caffeine groups when compared to the time required for control females. The etiology of this apparent reproductive effect is unclear.

Weathersbee et al. (Ref. 63) made a retrospective survey of 800 households identified by random sampling of medical records of women who had been obstetric patients in hospitals in Utah. Responses were obtained from 489 households. Approximately 75 percent of the individuals were Mormons whose use of alcohol, caffeine, and tobacco is proscribed. In 356 of the 489 households where presumably no caffeine, alcohol, or tabacco was used, there were 33 spontaneous abortions, 38 stillbirths, and 6 premature births, including 3 deaths. In 16 of the 489 households, when the woman's estimated mean daily caffeine intake was 686 mg (approximately 11 mg/kg/day) and the man's 566 mg, there were 8 spontaneous abortions, 5 stillbirths, and 2 premature births with no deaths. In 13 of the 489 households, where the woman's estimated mean daily caffeine intake was less than 400 mg (about 6.7 mg/kg/day) and the man's more than 600 mg, there were 4 spontaneous abortions, 2 stillbirths, and 2 premature births, with 1 death. In 23 of the 489 households, where mean daily caffeine intake by the man or woman was no more than 450 mg (about 7 mg/kg/day), there were no abortions, stillbirths or premature births.

Several factors weaken this study. There is a lack of attention to the fact that 311 of the 800 households selected did not participate. A variety of variables that could affect the results were not analyzed, including a comparision of Mormon women versus non-Mormon women and the differences between women who gave birth in hospitals and those who did not. In addition, the lack of a specific determinatin of caffeine consumption by women makes reliance on this study questionable. The authors concluded that a cause-and-effect relationship could not be established by this study, but suggested that excessive intake of caffeine might be a factor in spontaneous abortion and perinatal mortality.

2. *Conclusion.* The effects of caffeine on reproductive functions vary from study to study. In most of the animal studies, effects were seen only at levels of exposure significantly higher than humans would experience. The exception is the Palm study (Ref. 22). The effects seen in the Palm study at dose levels of 30 to 38 mg/kg deserve further research, but, because the animal used in the Palm study was the rat, the same questions apply here as were discussed above regarding the ability of rat data on caffeine to predict human response. The human study cited above, though adequate to raise questions worthy of further research, is also inconclusive. In sum, there is insufficient evidence to conclude that caffeine adversely affects the reproductive function in humans.

D. Carcinogenicity

1. *Animal and human data.* In a recent (1978) study by Takayama et al. (Ref. 64), the administration of 0.1 percent and 0.2 percent synthetic caffeine in the drinking water to groups of 50 male and 50 female Wistar rats was associated with a significantly increased incidence of tumors in caffeine-treated rats as compared to control animals receiving no caffeine. Significant increases in mammary adenomas and carcinomas and pituitary adenomas were observed in females given 0.2 percent caffeine. There was also a significant increase in mammary adenomas and pituitary adenomas in females given 0.1 percent caffeine. Males given 0.1 percent caffeine had a significant increase in pituitary adenomas. The incidence of adenomas and carcinomas of the thyroid was increased at both dose levels of caffeine in both sexes. There was a high incidence of uterine adenomas and carcinomas in females given 0.1 percent and 0.2 percent caffeine.

FDA has sought additional information on this study and has learned from the author that pneumonia seriously affected the survival rates of the test animals. The author also concluded that there was a nonlinear dose response found in the 0.1 and 0.2 percent test groups and that the results can only be considered preliminary. This study is being repeated (Ref. 65). FDA's Cancer Assessment Committee, located in FDA's Bureau of Foods, has reviewed this study and other available chronic studies of caffeine. FDA does not consider the Takayama study to be a conclusive study on the carcinogenicity of caffeine due to a lack of data relating to the design and conduct of the study. The reported nonlinearity of the results and the increased mortality among the test animals are not, however, sufficient reasons for rejecting the study. In the case of the dose response, the doses were close together and the early mortality from pneumonia among the test animals may have only lessened the chances for development of cancer in that group. FDA asked for additional information on the design, conduct, and results of this study from its author, but has not received sufficient information to permit reliance on the study as a definitive study on the carcinogenicity of caffeine.

In another recent study (Ref. 66), no increase in neoplastic or preneoplastic lesions was observed in groups of 20 male Osborne-Mendel rats given 0.5 percent caffeine in the diet for up to 75 weeks. The animals in this experiment were sacrificed after 75 weeks, and thus the time for tumor formation may not have been long enough for carcinogenicity to be expressed. The quality and power of the study is further undermined by the fact that only one sex was studied and that the number of animals used was not sufficient by contemporary standards for carcinogenicity testing.

In two other studies, no increase in carcinogenicity was found in rats given rations containing instant coffee (Refs. 67, 68). The animals were on test for 2 years, and their rations contained up to

about 0.18 percent caffeine. In a lifetime study, mice given fresh brewed coffee instead of drinking water did not show an increased incidence of cancer (Ref. 69).

Human epidemiology studies have not demonstrated a causal relationship in humans between coffee drinking and cancer (Refs. 70, 71, 72, 73). Kihlman (Ref. 74) believes that most of the available evidence suggests that caffeine may have anticarcinogenic effects rather than being a carcinogen or co-carcinogen. However, a higher incidence of bladder cancer has been detected among coffee drinkers as compared to matched controls (Ref. 75), and a correlation has been perceived between coffee consumption and national mortality rates from carcinoma of the kidney (Ref. 76).

2. *Conclusion.* The data concerning the potential carcinogenicity of caffeine are inadequate and incomplete. There are no lifetime feeding studies available on caffeine that meet currently accepted toxicological testing criteria. The results of the unpublished study by Takayama, et al. (Ref. 64) suggest an association between exposure to caffeine and an increased incidence of tumors in rats, but, as noted earlier, the study is being repeated because of the problems the author identified. FDA agrees that the study should be repeated.

Other chronic and long-term animal studies have been performed, involving both caffeine and coffee as test substances, that, although not fully adequate by current standards, suggest that caffeine is not carcinogenic. Moreover, there are no acceptable epidemiological data linking human exposure to caffeine with a significant increased incidence of cancer. As explained further below, the agency believes that, in order to resolve the question of whether caffeine is carcinogenic, chronic feeding studies meeting current toxicological testing standards should be carried out in two rodent species.

Based on the currently available data, FDA cannot determine conclusively whether caffeine is, or is not, carcinogenic in animals. There is no adequate basis at this time, however, for concluding that caffeine poses any risk of cancer in humans.

E. Behavioral Effects

1. *Animal and human data.* The neuropharmacologic properties of caffeine have been under investigation for several decades. Numerous behavioral, neurochemical, and neurophysiological studies have been conducted to characterize the neuropharmacologic effects of caffeine in humans and in animals (Refs. 77, 78, 79). Most of these studies were designed to consider caffeine as a drug and have dealt with the acute or short-term (generally not longer than several weeks) effects of caffeine in the mature, adult organism. There is only limited information about the neurobehavioral effects of chronic or long-term exposure or about the effects on the young, immature organism.

In studies with adult animals, caffeine has been shown to exert varying effects on the neurochemical and neurophysiological systems and to influence such behaviors as learning and memory, motor performance, sensory function, and emotional reactivity at acute dose levels as low as 0.5 to 2.5 mg/kg (Refs. 80, 81, 82, 83). Recently, evidence of physiological withdrawal has been reported in rats following several weeks of parenteral exposure to caffeine (Ref. 84). Many of these neurobehavioral effects, with the notable exception of effects on intellectual ability, have also been shown to occur to some extent in humans following acute or short-term dosing. The usual active oral dose in man is approximately 200 to 240 mg caffeine (3 to 4 mg/kg). Its effects range from those considered therapeutically "desired," such as improved motor performance, decreased fatigue, enhanced sensory acuity, mild cerebral stimulation, or increased alertness, to those that are considered nominal or inconsequential side effects, such as irritability, nervousness, or prolonged time to fall asleep. In their review of the clinical literature, Weiss and Laties (Ref. 78) pointed out that, after acute doses of about 240 mg of caffeine and above, which clearly enhance performance, adult human subjects variably report such symptoms as nervousness, feverishness, irritability, headache, and disturbed sleep. There also occurred a significant increase in tremor. Several clinical reports described mild symptoms of withdrawal, primarily headache, following exposure to caffeine over a period of several weeks (Refs. 85, 86, 87).

Little experimental attention has been given to the consequences of prolonged dietary exposure to caffeine on the functional capacity of the nervous system. In a single study recently reported by Estler, *et al.,* (Ref. 88), caffeine was given in the drinking water to mice for 6 weeks at a daily dose of 150 mg/kg. In contrast to the effects of a single dose, prolonged exposure to the caffeine resulted in detrimental effects, including diminished capacity to perform exhaustive work (swimming) under stressful conditions, impaired thermoregulation, as well as reduced weight gain. Spontaneous activity was unaffected, and motor coordination was even facilitated. Similar detrimental effects on work capacity had been reported earlier (Ref. 89) following prolonged exposure to coffee.

Some additional insight into the potential health effects of prolonged use of caffeine or related xanthines in adult subjects can be obtained from the acute pharmacologic studies. For example, the fact that the physiological and psychological effects of a single dose of caffeine in humans were different for regular coffee drinkers and for abstainers suggests that some form of habituation or tolerance develops to the effects of caffeine from repeated exposure (Refs. 85, 86).

There are only limited empirical data that deal with the effects of caffeine on children and even less dealing with experimental animals exposed to caffeine early in life during the period of development. Most of the pediatric data have been obtained from studies attempting to determine whether caffeine, as a central nervous system stimulant, was useful in the treatment of the hyperkinetic disorder of childhood. Caffeine was usually given in capsule at daily doses of 150 to 240 mg for periods of 1 day to 3 weeks. The therapeutic efficacy of caffeine in comparison to other medication for hyperkinesis has, thus far, not been impressive. Notably, however, most of the investigators reported no accompanying adverse effects of the caffeine in the hyperkinetic subjects nor in normal children, who were included in a study by Reichard and Elder (Ref. 90) as a matched group of control subjects. one group of investigators (Ref. 91) did note slight pharmacological effects (undescribed) from caffeine. Neims and Aranda (Ref. 92) reported a study in which caffeine was given to treat apnea (temporry suspension of respiration) in premature infants over a period of several weeks. They concluded that high plasma concentrations of caffeine (5 to 18 mg per liter, and occasionally as high as 85 mg per liter) during the treatment of apnea do not predispose to neurological or intellectual impairment, and that infants are not more susceptible to the effects of caffeine than adults. This latter conclusion conflict, however, with the report by Levitt and O'Hearn (Ref. 93) that children appear to be relatively more sensitive than adults to the excitant effects of caffeine.

Only recently has any experimental information begun to appear about the

neurobehavioral effects of caffeine exposure in animals during the period of growth and development. A study in rats reported some variable effects on physical development and behavioral changes in the offspring of dams exposed to caffeine in drinking water during gestation and lactation (Ref. 94). In a similar study using mice, Dews (Refs. 95) reported only nominal treatment effects. Several clinical and experimental animal studies are currently underway, or in varying stages of completion, to investigate the consequences of short-term as well as long-term exposure to caffeine on the functional neurobehavioral development of the immature organism.

As discussed more fully above, in explaining its ultimate conclusion that caffeine in "cola-type beverages" should no longer be considered GRAS, FASEB placed primary emphasis on the potential behavioral effects of caffeine in children. FASEB pointed out that the concerns about the behavioral effects of caffeine are less for adults "* * * than for children where there can be chronic consumption of caffeine in cola-type beverages during the period of brain growth and development. It is during this period of plasticity that the developing central nervous system is most sensitive to the effects of all aspects of the environment. The estimated levels of caffeine intake at these ages are near those levels that are known to cause central nervous system effects in adults."

Although it acknowledged that the available data are not adequate to answer the question of whether chronic exposure to caffeine in "cola-type beverages" poses a potential hazard to children and others, FASEB stated that it "* * * views with concern the continued addition of caffeine to cola-type beverages, representing as it does a unique addition to food of a pharmacologically active central nervous system stimulant." FASEB said: "* * * there is a possibility that behavioral effects in children from infancy through adolesence exist, even though these potential effects are neither adequately documented nor are their consequences clear." FASEB said further that: "A series of rigorously controlled chronic studies in appropriate species, including fetal, neonatal, and growing animals, of the immediate and ultimate behavioral and cardiovascular effects of caffeine added to the diet and given in cola-type beverages, would reduce ares of speculation."

2. *Conclusion.* The discussion above concerning behavioral effects raises questions concerning the possibility that chronic exposure to caffeine in soft drinks may cause behavioral effects in children. These questions must be answered. Caffeine is the only pharmacologically active food ingredient known to FDA that is added to foods at levels that approximate those required to accomplish its pharmacological effect, in this case stimulation of the central nervous system. As FASEB pointed out, the presence of this ingredient in beverages to which children may be chronically exposed during their early developmental years raises substantial questions from a health point of view. Data from animal studies suggest that even very low (0.5 to 2.5mg/kg) acute dosage levels can influence such behaviors in test animals as learning and memory, motor performance, sensory functions, and emotional reactivity (Refs. 80, 81, 82, 83).

The problem, of course, it that very little is known about what type of behavioral effects, if any, actually occur in human infants and young children as a result of chronic, low-level exposure to caffeine; and even less is known about what significance such effects would have, if any, in terms of actual harm to children. Methods for identifying and measuring such effects and assessing their significance are not as well developed as those used to identify and assess the more conventional toxicities (e.g., acute toxicity, mutagenicity, teratogenicity, and carcinogenicity). This is due in part to the fact that, traditionally, toxicologists simply have not focused much of their attention on the potential behavioral effects of food ingredients. Another reason for the lack of attention and knowledge in this area is that pharmacologically active substances, which are most likely to pose concerns about behavioral effects, are rarely added intentionally to food; as noted earlier, caffeine may be unique in this regard. For these reasons, a broad range of additional studies is needed to identify more completely the neurophysiological effects of chronic, low-level exposure to caffeine in the young and to determine the impact of these effects on children's development and behavior.

F. Functionality

Questions must be resolved not only about the safety of caffeine but also about its functional effect as an added food ingredient. Questions about the functional effect of caffeine must be addressed because it is the policy enunciated by Congress (section 409(c)(4), 21 U.S.C. 348(c)(4)) and FDA's regulations (§ 172.5(a)(1) (21 CFR 172.5(a)(1))) that substances not be used in food in an amount that exceeds that reasonably required to accomplish the intended physical, nutritive, or other technical effect. In practice, this means that caffeine must have an identified purpose or function as an added ingredient in soft drinks and other foods and be capable of accomplishing that purpose or function at the levels at which it is used. The health purpose underlying this requirement is to preclude the needless addition of chemicals to food.

The questions that must be answered about added caffeine's functionality stem from the uncertainty about the purpose for which added caffeine is used in soft drinks and other foods. Food manufacturers, responding to the NAS/NRC survey of food manufacturers, report that caffeine is used as a flavor enhancer, flavoring agent, and synergist in soda water beverages (Ref. 96). All three of these functions are recognized by FDA's regulations (§ 170.3(e)(11), (12), and (31) (21 CFR 170.3(o)(11)(12), and (31), respectively)). In addition FDA knows that kola nut extract, which contains about 2.35 percent caffeine, is used as a flavor ingredient in cola-type soft drinks (Ref. 97). However, the amount of kola nut extract needed for flavoring provides less that 10 percent of the caffeine normally present in colas. It is not known whether the other 90 percent or more of the caffeine added to cola beverages has any flavoring effect. The only other known functional effect of caffeine in food is central nervous system stimulation. This function was not identified by food manufacturers in the NAS/NRC survey as an intended function, but the Food Chemicals Codex (2d Ed., 1972) lists the functional use of caffeine as a "central stimulation in cola-type beverages." (Ref. 2).

As discussed above, caffeine is a drug. In addition, it is the only pharmacologically active food ingedient known to FDA that is added to foods at levels that approximate those required to stimulate the central nervous system. Although it is inclear whether FDA has authority under the law to prohibit the use of a food ingredient solely because the ingredient is a stimulant, the use of any pharmacologically active substance as a food ingredient raises serious public health questions, especially where, as in the case of caffeine, the foods involved are consumed widely by children. Given these facts, FDA places great importance on identifying all the intended uses of added caffeine, especially in soft drinks, and determining whether the amount of caffeine being added to foods is

necessary, or even useful, to accomplish the intended physical, nutritive, or other technical effects. Thus, as a condition to the continued use of caffeine in soft drinks and other foods, manufacturers will be required under the regulation FDA is proposing in this document to develop and submit to FDA data that (1) fully describe the purposes for which caffeine is added (including a delineation of the claimed "synergistic" effect), and (2) demonstrate that the amounts of caffeine being added are necessary and effective for these purposes.

V. Discussion of Options and Rationale for Proposed Action

After evaluating the existing data concerning caffeine as an added food ingredient, FDA considered which of several possible regulatory actions would be most appropriate. As discussed briefly in Section II above, the law provides the agency with three options. It can propose to affirm the GRAS status of caffeine as an added food ingredient, essentially maintaining the status quo. Alternatively, it can propose to delete added caffeine from the GRAS list and declare that added caffeine is an unapproved food additive that cannot be used in food until a regulation authorizing its use is promulgated in accordance with section 409 of the act, effectively banning added caffeine until the questions about its safety have been resolved. Finally, the agency can propose to delete added caffeine from the GRAS list but permits its continued use as an interim food additive under Part 180 (21 CFR Part 180) pending completion of the studies required to resolve the questions raised about its safety and functionality. The availability of these last two options depends as a legal matter, of course, on FDA's conclusion that the current uses of caffeine are not subject to any prior sanctions and thus that if added caffeine loses its GRAS status, it is a food additive. As noted earlier in this document, FDA is proposing to declare that no prior sanctions exist for added caffeine; but, if acceptable evidence of a prior sanction for a specific use of added caffeine is submitted in response to this proposal, FDA will propose to recognize that prior sanction and will not include that use of added caffeine in any final version of the proposed interim food additive regulation.

Based on the existing data, including the data specifically discussed in this document, FDA concludes that it would be inappropriate to affirm the GRAS status of caffeine as an added food ingredient. Under the statute, 21 U.S.C. 201(s), and FDA's regulations, 21 CFR 170.30, GRAS status is reserved for those food ingredients for which adequate data to establish safety not only exist but are commonly known throughout the segment of the scientific community that is knowledgeable about the safety of substances added to food. Under this standard, a substance cannot be GRAS if the existing data are not adequate to resolve substantial questions of safety raised by knowledgeable scientists. Although the existing data do not demonstrate a hazard to consumers from caffeine as an added food ingredient, they do raise substantial safety-related questions that must be resolved by further study. Moreover, if caffeine were to retain its GRAS status, FDA would have no mechanism for compelling the resolution of the safety questions discussed above. For these reasons, FDA is not proposing to affirm the GRAS status of added caffeine.

FDA has considered whether it would be appropriate, at this time, to prohibit future use of added caffeine by declaring it to be an unapproved food additive. The agency is proposing to reject that course. Although the existing data raise questions about the safety of caffeine, they do not demonstrate that a hazard to the public actually exists. As science progresses and as new studies are performed, it is common for questions to be raised about the safety of food ingredients. In most cases, these questions can be resolved satisfactorily by additional studies. As long as there is a reasonable certainty that no harm to the public will result from the continued use of the substance for the limited period of time required to resolve the questions, it would be inappropriate to ban the substance while the questions are being resolved. Otherwise, bans could become common occurrences, severly disrupting the food supply without a substantial likelihood of enhancing public health protection. In the case of added caffeine, FDA's judgment is that the public will be protected adequately without an immediate ban. As explained in Section IV, the existing data on caffeine raise questions about its safety, but do not demonstrate any actual risk to humans.

This leaves the last option, which FDA is proposing to adopt (assuming no prior sanction exists): deletion of added caffeine from the GRAS list and regulation of it as an interim food additive pending completion of the necessary studies. See 21 CFR 180.1 *et seq.* In proposing this course of action, FDA has carefully analyzed all the safety and functionality data available to it and, for the reasons discussed in Section IV, has concluded that substantial questions have been raised, but there is a reasonable certainty that the substance is not harmful and that no harm to the public health will result from the continued use of the substance for a limited period of time.

A primary advantage of interim regulation is that it permits FDA to require the sponsor of a substance about which questions have been raised to perform the studies necessary to resolve the questions. Performance of the studies is a condition to continued use of the substance under the interim regulation (21 CFR 180.1(c)(2)). The studies the agency is proposing to require on caffeine are described in Section VII below. These studies should resolve the existing questions about both the safety and functional effect of caffeine as an added food ingredient. The legality of FDA allowing continued use of a food additive on an interim basis while required studies are being performed has been reviewed by both the U.S. District Court and the U.S. Court of Appeals for the District of Columbia. Both have held that such an approval, given certain factual findings, is an appropriate exercise of FDA's authority. *Jacobson* v. *Edwards,* No. 445–71 (D.D.C. 1971); *aff'd* No. 71–2046 (D.C. Cir. 1972) (reported at ¶ 40,817, CCH F.D. Cosm. L. Rep.).

As mentioned above, added caffeine is currently being used in several nonbeverage food categories on the basis of an independent determination by the Flavor Extract Manufacturers' Association that caffeine is GRAS for those uses. In the course of its safety review of caffeine as an added ingredient in soft drinks, FDA has evaluated the GRAS status of caffeine for its nonbeverage uses and concludes that those uses can no longer be considered GRAS. This conclusion is based on the same data and safety concerns that justify removing caffeine in soft drinks from the GRAS list and regulating it as an interim food additive. Thus, the interim food additive regulation the agency is proposing will include the current nonbeverage uses of caffeine. When the interim food additive regulation becomes final, any uses of caffeine as an added food ingredient that are not included in the regulation will be considered unlawful.

In addition to requiring the performance of specified studies concerning the safety and functionality of caffeine, the interim regulation will require that the label of any finished food product containing added caffeine include "caffeine" in the statement of ingredients. FDA recognizes that flavors

are generally not required to be identified by name in ingredient statements (see sections 403(g) and (i) of the act (21 U.S.C. 343(g) and (i)) and §§ 101.6(b) and 101.22(h) (21 CFR 101.6(b))) and 101.22(h) and that caffeine is claimed to be used for a flavoring purpose. The food additive provisions of the act, however, authorize the agency to impose whatever labeling requirements it deems necessary to ensure safe use of an additive (see section 409(c)(1)(A) of the act, 21 U.S.C. 348(c)(1)(A)). The ingredient labeling requirement for caffeine will help ensure safety because it will make it easier for consumers to limit their exposure to caffeine in food. This can be particularly important from a safety standpoint for consumers who are already experiencing significant exposure to caffeine in coffee, tea, or chocolates, or in drug products, or who may need to exercise particular caution about consuming any pharmacologically active substances, such as pregnant women. As will be discussed further in response to a citizen's petition FDA has received concerning caffeine, the agency does not believe that the data raising safety questions are strong enough to justify requiring warning labels at this time for all food products containing caffeine. FDA is thus limiting its proposal dealing with the labeling of food products containing caffeine to that discussed above.

In an action that is related to the proposal to delete added caffeine from the GRAS list, FDA is proposing (in a separate document published elsewhere in this issue of the **Federal Register**) to amend the soda water standard in § 165.175 (21 CFR 165.175) to make caffeine an optional, rather than mandatory, ingredient in cola- and pepper-type soft drinks. This amendment is intended to encourage the reduction or elimination of caffeine use in these types of soft drinks.

FDA is proposing no action in this document regarding the drug products that contain caffeine, though the agency recognizes that substantial exposure to caffeine can result from the use of these drugs. The agency is in the process of considering what, if any, action is appropriate regarding caffeine-containing drug products, including possible labeling changes, based on the information currently available.

VI. Response to Minority Opinion

One member of the FASEB committee that reported to FDA on caffeine, Dr. Ralph G. H. Siu, submitted a minority opinion in which he differed with the majority's evaluation of the existing data on caffeine in soft drinks and argued that any official regulatory action concerning caffeine should be deferred pending completion of a comprehensive review of the safety of caffeine consumption from all sources, including coffee and tea (Appendix, Ref. 6). This section responds to Dr. Siu's views.

Based on its review of the biological data on caffeine, the FASEB majority concluded: "While no evidence in the available information on caffeine demonstrates a hazard to the public when it is used in cola-type beverages at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies be conducted." Dr. Siu, however, expressed a somewhat greater degree of concern about the potential hazards posed by the use of added caffeine than the majority expressed. Like the majority, Dr. Siu did not conclude that the use of caffeine in "cola-type beverages" does in fact pose a hazard to the public. He found, instead, that: "The evidence on caffeine in cola-type beverages is insufficient to determine that the adverse effects reported are not deleterious to the public health when it is used at levels that are now current and in the manner now practiced."

As the basis for this conclusion, Dr. Siu cited several factors that parallel the concerns cited by the majority: caffeine is a widely used, psychotropic drug that acts as a central nervous system stimulant; it is the only drug consumed chronically in food at pharmacologically active levels; it has been shown in animal studies to affect a "broad array of biochemical and physiological processes;" and it is "embroiled in a number of disagreements over its potential contributions to clinical disorders." In discussing potential "clinical disorders," Dr. Siu placed more emphasis on the potential cardiovascular effects of caffeine than did the majority. In addition, Dr. Siu noted that caffeine "participates in metabolic processes in a broad and central sense in its influence on the equilibrium content of adenosine 3', 5'-cyclic monophosphate (cyclic-AMP) in the tissues." The majority did not report this effect on cyclic-AMP as one of the factors bearing on its conclusions about caffeine.

In each instance, Dr. Siu stopped short of finding that the data demonstrate an actual hazard to the public from the consumption of "cola-type beverages," but he identified several areas in which he felt existing data left particularly large areas of uncertainty. For example, in discussing the effects caffeine has on various biochemical and physiological processes, Dr. Siu said: "When singly assessed, most of these changes may with some justification be looked upon as innocuous. * * * Yet the uncertainty keeps gnawing away at the safety assurances that can be offered in the face of potential synergistic concatenations of alterations, one or more of which may initiate an unhealthy cascade." Addressing another area of concern, Dr. Siu agreed that no cause and effect relationships had been definitively established between exposure to caffeine and such "clinical disorders" as heart ailments, ulcerogenesis, mutagenicity, teratogenicity, and carcinogenicity. He spoke, however, of the need for further study to resolve the question of caffeine's potential to cause adverse effects among those who are especially susceptible to a particular effect or experience an unusually high level of exposure to caffeine.

FDA finds nothing in Dr. Siu's discussion of the available evidence on caffeine that is inconsistent with the agency's decision to propose deleting caffeine from the GRAS list and regulating it as an interim food additive. Indeed, Dr. Siu's discussion of the data supports FDA's conclusion that caffeine should no longer be considered GRAS and that additional studies are needed to resolve certain safety questions. The agency believes that the additional studies it proposes to require will provide answers to most, if not all, of the questions raised by Dr. Siu.

Ironically, Dr. Siu's apparently more serious reservations about the safety of added caffeine do not lead him to recommend more stringent regulatory actions than the FASEB majority recommended. Instead, Dr. Siu recommends that the agency defer any action on the GRAS status of caffeine as an added food ingredient: "Official reevaluation of the potential health hazard of caffeine in cola-type beverages alone should be kept open until an assessment of the safety of its consumption in all foodstuffs, individually and collectively, is completed with appropriate participation by all interested parties." (Appendix, Ref. 6). Dr. Siu makes two points in support of this recommendation.

He notes first that "cola-type beverages" are only one source of caffeine exposure and, in fact, by his estimate, account for only about a fourth of total caffeine exposure from foodstuffs (the other primary sources being, of course, foods such as coffee, tea, and chocolate that contain naturally occurring caffeine). Based on that fact,

he contends that considering the safety of caffeine only as it is consumed from soft drinks "constitutes such an artifically bounded abstraction that the resulting conclusions can only be of limited, and even misleading, operational meaningfulness in real life." Dr. Siu's point here seems to be that ultimate judgments about the safety of dietary caffeine should be based on a consideration of caffeine exposure from all dietary sources.

Dr. Siu's second point is that "to pass judgment on cola-type beverages alone at this time may be prejudicial to coffee and other caffeine-containing foodstuffs, representatives of which had not been explicitly forewarned and who, as a consequence, had not come forward with their own data and opinion." Dr. Siu contends that any agency judgment on the safety of caffeine as an added food ingredient effectively (and unfairly) prejudges the safety of other foods, such as coffee and tea, that contain naturally occurring caffeine.

For the reasons discussed below, FDA considers the action being proposed in this document to be an appropriate and significant step toward Dr. Siu's, and the agency's, goal of a comprehensive resolution of the caffeine question.

As noted in Section II above, the purpose of the GRAS review process, out of which this document arises, is to reevaluate by modern toxicological standards, and in light of the data now available, the safety of substances that FDA had placed on the original GRAS list in the late 1950's and the early 1960's. Caffeine as an added ingredient in cola-type beverages was one such substance (see 21 CFR 182.1180); naturally occurring caffeine was not. It was thus appropriate, and in keeping with its mandate from FDA, for FASEB to focus in its recommendations on the added uses of caffeine.

As Dr. Siu correctly suggests, however, the data that make necessary a change in the regulatory status of added caffeine also raise questions about the safety of caffeine as a natural constituent of coffee, tea, chocolate, etc. These are questions that FDA must be, and is, concerned about, especially since, as Dr. Siu points out, coffee and tea account for a very substantial portion of total dietary exposure to caffeine. However, the agency faces difficulties in dealing with naturally occurring caffeine.

One of the difficulties the agency faces, and one of the primary reasons this document deals only with added caffeine, is that naturally occurring caffeine is subject to regulation by FDA on a singificantly different legal basis than is added caffeine. Unlike added caffeine, naturally occurring caffeine is not itself subject to regulation under the food additive provisions of the law (21 U.S.C. 321(s) and 409). Thus, the question of GRAS status, which FASEB and FDA have considered and answered in this proceeding with respect to added caffeine, is simply not legally relevant to naturally occurring caffeine.

FDA's traditional practice has been to regulate inherent constituents of food, such as naturally occurring caffeine, as naturally occurring "poisonous or deleterious substances" under the general adulteration provisions in section 402(a)(1) of the act (21 U.S.C. 342(a)(1)). Under those provisions, the question is not whether naturally occurring caffeine is GRAS but whether FDA can show that caffeine renders the foods in which it naturally occurs "ordinarily injurious to health." That is a burden the agency does not believe it can sustain on the basis of existing data because the data do not establish that foods containing naturally occurring caffeine cause injury when consumed in ordinary amounts by the average consumer. Thus, it would be premature for the agency to propose action now involving naturally occurring caffeine as a "poisonous or deleterious" substance.

In recommending that FDA defer any regulatory action involving added caffeine, the FASEB minority report overlooks the legal distinction between added and naturally occurring caffeine and fails to consider the limited nature of the action recommended by FASEB and proposed here by FDA. FDA proposes no restrictions on the current marketing of caffeine in any form, but rather proposes to require additional studies that will address and hopefully resolve the question of caffeine's safety as both an added and naturally occurring constituent of food. FDA's authority to require studies flows from the food additive provisions of the act, which apply directly only to the added uses of caffeine. It is thus appropriate that the legal focus of this proposal be on added caffeine.

The minority report's concern that this action on caffeine might amount to an unfair prejudgment on the safety of naturally occurring caffeine is unwarranted. The deletion of added caffeine from the GRAS list and regulation of it as an interim food additive is, by its very nature, an intermediate step. It is intended to lead to, but it is not based upon, final judgments about the safety of caffeine, whether added or naturally occurring. Final judgments about added caffeine will likely not be made at least until the required studies are completed. At that time, any interested person, including those concerned about the legal status of naturally occurring caffeine, will have an opportunity to participate and to present their views. At this point, the important concern is to begin the necessary studies.

For the foregoing reasons, FDA declines to adopt Dr. Siu's recommendation that the proposed action on added caffeine be deferred.

VII. Response to Citizen Petitions

During the course of FDA's review of the safety and regulatory status of added caffeine, which FDA initiated as part of its GRAS review program, the agency received several citizen petitions, filed unde 21 CFR 10.30, urging that certain regulatory actions be taken regarding caffeine. At the time these citizen petitions were received, FDA was actively reviewing added caffeine's regulatory status, and therefore each petitioner received a proper tentative response pursuant to 21 CFR 10.30(e)(2)(iii). Those responses generally advised each petitioner that the substance of their requests was already under active review by FDA and that the appropriate decisions would be forthcoming from the agency when the ongoing review was completed. FDA's proposals to issue an interim food additive regulation for added caffeine and to amend the standard of identity for soda water represent the agency's proposed regulatory actions resulting from that review. FDA will now provide further responses to several pending citizen petitions.

The Federation of Homemakers, Arlington, Virginia, submitted two petitions on caffeine. The first petition (No. 79P–0343/CP) requested FDA to "remove, delete and strike caffeine from the list of GRAS Food Substances, because it is not generally recognized as safe." The petition quoted the conclusion of the FASEB report on caffeine in support of the requested action (Ref. 98).

FDA indicated earlier in this document that, based on its own careful evaluation of the available safety data on caffeine, it proposes to concur with the majority conclusions of the FASEB report on caffeine, including FASEB's conclusion that caffeine added to soft drinks should no longer be considered GRAS. Therefore, FDA is proposing to delete caffeine from the list of GRAS substances in Part 182 (21 CFR Part 182), thereby granting the Federation of Homemakers first petition to the extent it can consistent with the rulemaking requirements of the administrative Procedures Act and FDA's own

procedures. A final agency decision on the GRAS status of added caffeine must, of course, await completion of this rulemaking process (see 21 CFR 170.3 et seq.). As set out in detail in this document, FDA not only proposes to remove added caffeine from the GRAS list as the Federation of Homemakers requests, but also to place it in the correct regulatory status as an interim food additive (21 CFR 180.1).

The second petition from the Federation of Homemakers (No. 79P–0344/CP) seeks to change the standard of identity for soda water (21 CFR 165.175) so as to remove added caffeine from all soda water and to limit the caffeine content of cola-type beverages to that present in kola nut extract and/or other natural caffeine-containing extracts. Under the petition, such caffeine would be an optional ingredient present in only "trace" amounts (Ref. 99).

FDA is proposing amendments to the soda water standard in a notice appearing elsewhere in this issue of the **Federal Register.** These proposed amendments are intended to accomplish the following: (1) declare that kola nut extract, not caffeine, is the mandatory ingredient in "cola" and "pepper" beverages; (2) provide for a caffeine-free "cola" or "pepper" beverage consistent with the standard; and (3) clarify the fact that added caffeine as such is an optional ingredient rather than a mandatory one, but that, as an optional ingredient, it may continue to be used.

Food standards are promulgated under section 401 of the act, 21 U.S.C. 341. The statutory standard that applies to the promulgation of any such standard is that such action "* * * will promote honesty and fair dealing in the interest of consumers * * *." The process by which a food standard is developed or amended does not normally encompass fundamental safety assessments of the proposed ingredients. The food and color additive provisions provide the statutory mechanism for the safety evaluation of such ingredients (21 U.S.C. 348 and 376, respectively). Only ingredients that are in compliance with those sections, or are otherwise exempt due to their GRAS or prior-sanctioned status, are lawful in foods for which a standard has been promulgated. FDA is proposing in this document to allow the continued use of added caffeine pursuant to an interim food additive regulation. Because added caffeine will, if the proposal is finalized, still be lawful, FDA does not believe that an adequate basis exists at this time to preclude the use of added caffeine as an optional ingredient under the standard of identity and therefore denies the Federation of Homemakers petition seeking that result.

Despite FDA's belief that added caffeine should still be allowed as an optional ingredient in these beverages, the proposed amendments to the standard of identity will allow consumers more choice in the types of "cola" or "pepper" beverages available. Even if the safety questions regarding this use of caffeine are resolved in favor of its continued use, there is an unquestioned stimulant effect from the substance. This is an effect that some consumers may wish to avoid. Allowing those consumers the freedom to choose caffeine-free "cola" or "pepper" beverages under the soda water standard clearly promotes honesty and fair dealing in the interest of consumers.

The Center for Science in the Public Interest (CSPI), Washington, DC, also has submitted a petition (No. 79P–0443/CP) concerning caffeine. The petition requests that FDA (1) issue a regulation requiring that all packages of tea and coffee that contain caffeine carry a plainly visible warning advising that consumption of the product may be harmful to the unborn children of pregnant women, and (2) initiate an educational campaign designed to inform pregnant women about the ability of caffeine to interfere with reproduction (Ref. 100). The petitioner submitted selected data on caffeine consumption by pregnant women, as well as animal and human epidemiologic data on caffeine, that the petitioner believes is an ample basis upon which to require a warning label for coffee and tea. Without such a warning, the petitioner contends that all these products are misbranded since their labels are false and misleading pursuant to 21 U.S.C. 343(a). The petition contends that the potential teratologic effects of caffeine are a "material" fact within the meaning of 21 U.S.C. 321(n) and thus that without a warning concerning this effect, these labels are, at least, misleading. FDA disagrees with this conclusion both as a matter of fact and law. As discussed below, the agency does not feel that sufficient data exist, at this time, to require such a warning.

FDA's legal authority to require a warning label on packages of coffee and tea is derived from the misbranding provisions of the Federal Food, Drug, and Cosmetic Act, which deem unlawful, among other things, any food that bears a label which is either false or misleading (21 U.S.C. 343(a)). In further defining the term "misleading," the statute states (21 U.S.C. 321(n)):

> (n) If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, *but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.* [Emphasis added].

The statute provides the agency with the discretionary authority to enforce these provisions in a reasonable manner as it sees fit. The agency can either take judicial enforcement action against such products under sections 302, 303, and 304 of the Act (21 U.S.C. 331, 333 and 334) or initiate a rulemaking proceeding to require labeling to ensure that the food is not in violation of these statutory provisions. In either case, the burden of proof is on the agency to establish that the labeling is justified or the judicial relief requested is appropriate. This situation, where the agency has the ultimate burden of proof, must be contrasted with those statutory provisions where the agency need only raise questions or "new evidence" before the ultimate burden of proof shifts to the manufacturer. (See, for instance, the provisions for removal of a new drug, 21 U.S.C. 355(e) or new animal drug, 21 U.S.C. 360b(e).

As discussed earlier in this document, FDA does not believe that sufficient evidence exists at this time to link caffeine and an increased risk of birth defects in humans, but the agency is proposing to require the additional studies it feels are needed to better understand the human response to caffeine. Due to the state of the currently available evidence and the fact that more conclusive evidence is in the process of being obtained, FDA does not consider it appropriate at this time to require the type of warning label on caffeine-containing coffee and tea products requested in the CSPI petition.

This is not to say that the data presented by the petitioner, as well as the additional data discussed in this document, do not raise health-related questions concerning the use of caffeine, especially by pregnant women. They do raise such questions, and it is for that reason that FDA is proposing to take the regulatory action described in this document. These questions must and will be answered. Comments received on FDA's proposed regulatory action or the additional studies the agency is

proposing to require may well provide the basis for the type of warning suggested by the petitioner. At this time, however, based on available data, the agency does not feel that it would be a reasonable or justifiable exercise of its discretion to require a warning label.

As for CSPI's second request, which is to initiate an education program directed at pregnant women to educate them concerning caffeine, FDA has concluded that certain such steps are appropriate at this time. As just discussed, the requirement of warning labels on each specific caffeine-containing coffee and tea product requires a level of evidence FDA does not believe exists on caffeine. However, the fact that the questions concerning the safety of caffeine do not provide a basis for specific product labeling does not preclude the agency from providing the public, especially pregnant women, with cautionary advice based on the scientific evidence available to date concerning caffeine. The public has an inherent right to be informed fully about the food they ingest so that they may, if they so decide, avoid foods about which safety questions have been raised. To that end, the Commissioner of Food and Drugs announced on September 4, 1980, a campaign to provide the public with information concerning the possible adverse effects of caffeine (Ref. 101). the Commissioner announced the following:

> Advice about caffeine use during pregnancy will be communicated through all PHS programs that serve pregnant women, maternal and child health projects, community health centers, migrant health and Indian health programs, and in PHS hospitals and clinics.
>
> The Surgeon General will write to health professional organizations such as the American Medical Association and the American College of Obstetricians and Gynecologists to urge them to notify their members of the latest scientific information.
>
> The Food and Drug Administration will carry this same message to health professionals through its Drug Bulletin and to the public through publications such as FDA Consumer magazine.

In addition, other mechanisms of disseminating this information, as well as ways to assess the effectiveness of this program, are being explored. FDA agrees with the petitioner that information on caffeine should be made publicly available, and it is acting accordingly.

VIII. Required Studies

The continued use of added caffeine under the proposed interim food additive regulation is conditioned on the performance of studies necessary to resolve questions concerning the safety and functionality of caffeine as an added food ingredient. The studies that must be performed are described in proposed § 180.15(e). Additional studies may be required at a later date if they are found necessary to resolve questions raised, or not completely resolved, by the studies described in proposed § 180.15(e). FDA attaches particular importance to resolution of the question of the teratogenic potential of caffeine in humans (§ 180.15(e)(2)). The currently existing information relating to the teratogenic effects of caffeine provides an insufficient basis to determine whether caffeine *per se* and/or one of its metabolites is the causative agent for the teratogenic effects observed in experimental animals. Studies addressing this question need to be conducted. It is also important to determine through appropriate pharmacokinetic and metabolic studies the differences between the ways caffeine is handled by humans and animals, and specifically, whether any of the known metabolites of caffeine that may be teratogenic in experimental animals are formed by humans. Also, if unique metabolites are formed by humans, it is important to determine whether these compounds are teratogenic or otherwise toxic in experimental animals. During the period that these studies are being carried out, FDA also will require that appropriate epidemiology studies be carried out (§ 180.15(e)(6)). The details of the design and performance of these studies should be worked out in consultation with the FDA.

It is recognized that this will require an extensive program of synthesis and testing of a large number compounds. The precise sequence and design of the studies is a matter on which FDA specifically solicits comments. The agency is prepared to work closely with those conducting the needed research to ensure that it is done in a logically ordered, well-focused manner calculated to resolve the outstanding questions as efficiently and promptly as possible.

FDA shares the concern of FASEB about the neurobehavioral effects of caffeine consumption in young children. Information is needed concerning the immediate and latent effects of prenatal and postnatal exposure to caffeine on the functional development of the immature nervous system (§ 180.15(e)(3)). Special attention should be given to the effects of prolonged or continous exposure to caffeine in the developing offspring. The neurobehavioral testing should consider multiple criteria of nervous system function, including behavioral, neurophysiological, and morphochemical measures. Both clinical studies with children and experimental studies with suitable animal species should be conducted. Clinical studies should identify and make use of intake levels of caffeine. In addition to data on the effects of caffeine in the developing organism, additional clinical and experimental information is needed concerning the neurobehavioral sequellae of prolonged or continuous exposure to caffeine in the adolescent, adult, and aged organisms, with some attention being given to the withdrawal phenomenon. Selection of the appropriate animal models for these studies should await completion of the studies needed to better understand the coparative metabolism and pharmacokinetics of caffeine in animals and humans.

In order to reflect the usual mode of exposure in man, the studies should use the diet (i.e., feed or drinking water) as the principal route of administration of caffeine. However, some attempt should be made to determine whether the neurobehavioral effects from prolonged dietary intake, whch generally results in exposure being spread out over the entire day, are substantially different from those resulting from repeated intubation, as might occur when one rapidly drinks a bottle of a caffeine-containing soft drink.

FDA understands that several studies of the possible carcinogenicity of caffeine are currently underway. Thus, rather than require that additional studies be undertaken immediately, the agency is proposing to require initially that persons who intend to rely on the ongoing studies to demonstrate the safety of caffeine submit details of the design and conduct of the studies to FDA (proposed § 180.5(e)(4)). This will allow the agency to determine if the on-going studies are found to be deficient by current standards, additional studies will be required.

To adequately resolve the carcinogenicity question, and also determine whether caffeine can cause other long-erm effects (proposed § 180.15(e)(5)), chronic feeding studies meeting current toxicological testing standards must be carried out in two appropriate species. Such studies should be designed to test for carcinogenicity as well as other possible chronic pathologic effects. At least one of the studies should involve in utero exposure, and both studies should include feeding of at least three dose levels of caffeine. In addition, a 1-year feeding study involving feeding of at least three dose levels of caffeine should

be carried out in the dog or other appropriate nonrodent species.

Due to the uncertainty about the purpose(s) for which caffeine is added to various foods and about whether caffeine is effective for its claimed flavoring purpose, the agency is proposing to require that data be developed and submitted to FDA that (1) fully describe the purpose(s) for which caffeine is added to each food covered by the interim regulation, and (2) demonstrate that the amount of caffeine added to each food is necessary and effective for each purpose(s) (proposed § 180.15(e)(7)). In the case of cola- and pepper-type soft drinks, in which kola nut extract is a mandatory ingredient, the functionality data should distinguish clearly between the caffeine that is present as a component of the kola nut extract and the caffeine that is added over and above that present in kola nut extract. It is the latter caffeine whose functionality must be demonstrated.

In accordance with § 180.1 (21 CFR 180.1), the primary responsibility for performing the required studies on caffeine rests on interested persons outside the agency. FDA will, however, work closely with those who agree to undertake the required studies to help ensure that the studies are designed and executed in a way that will be most likely to produce the scientific evidence needed to resolve the existing safety questions about caffeine. If the appropriate commitment to undertake the required studies, or submit the required data and information, are not made to FDA within 60 days after the effective date of a final regulation based on this proposal, an order shall be published immediately in the Federal Register revoking the interim food additive regulation effective upon publication (see § 180.1(c)(2)). Similarly, the interim regulation will be revoked if persons performing the required studies fail to submit the twice-yearly progress reports required in § 180.1(c)(3).

The agency has determined under 21 CFR 25.24(b)(6) (proposed December 11, 1979; 44 FR 71742) that this proposed action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

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99. Citizen Petition, dated 8–30–79, from Federation of Homemakers, P.O. Box 5571, Arlington, VA 22205, FDA Hearing Clerk No. 78P–0344/CP.

100. Citizen Petition, dated 11–15–79, from Center for Science in the Public Interest, 1755 S St., N.W., Washington, D.C., FDA Hearing Clerk No. 79P–0443/CP.

101. Goyan, J.E. statement by the Commissioner of Food and Drugs, September 4, 1980, (P80–36), page 3.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs, 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784–1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and under authority delegated to the Commissioner of Food and Drug (21 CFR 5.1), it is proposed that Parts 180 and 182 be amended as follows:

PART 180—FOOD ADDITIVES PERMITTED IN FOOD ON AN INTERIM BASIS OR IN CONTACT WITH FOOD PENDING ADDITIONAL STUDY

1. Part 180 is amended in Subpart B by adding new § 180.15 to read as follows:

§180.15 Caffeine.

(a) Caffeine ($C_8H_{10}N_4O_2$ CAS Reg. No. 58–08–2) is the alkaloid 1,3,7-trimethylxanthine. Caffeine is prepared by extraction from coffee or tea, by partial synthesis from theobromine, by total synthesis from uria and cyanoacetic acid or by total synthesis from dimethyl carbamide and malonic acid.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 2d ed. (1972),[1] as amended by the First Supplement (1974),[1] which is incorporated by reference.

(c) The ingredient is used directly in food, as served, at levels not to exceed the following maximum levels:

Food categories	Parts per million (ppm)	Function
Soda water, section 165.175 of this chapter	200	Flavor enhancer, section 170.3(o)(11) of this chapter. Flavoring agent, section 170.3(o)(12) of this chapter. Synergist, section 170.3(o)(31) of this chapter.
Baked goods, section 170.3(n)(1) of this chapter	400	Flavoring agent, section 170.3(o)(12) of this chapter.
Frozen dairy desserts and mixes, section 170.3(n)(20) of this chapter.	400	Do.
Gelatins, puddings and fillings, section 170.3(n)(22) of this chapter.	400	Do.
Soft candy, section 170.3(n)(38) of this chapter	400	Do.

(d) To ensure safe use of the additive, in addition to other information required by the act:

(1) The label of the additive and any intermediate mix shall bear—

(i) The name of the additive; and

(ii) A statement of the concentration of the additive (expressed as "caffeine") in any intermediate mix, or other information to permit a food processor to determine independently that use of the ingredient will comply with this section.

(iii) Adequate directions for use to provide a final food product that complies with the provisions of this section.

(2) The ingredient statement of any finished food product containing the additive shall include the name of the additive, i.e., "caffeine".

(e) In accordance with § 180.1, adequate and appropriate studies shall be performed to resolve existing questions about the safety of the food additive. These studies shall include:

(1) Pharmacokinetic studies, both acute and chronic, in human volunteers and in appropriate animal species, including the rat, to determine the comparative patterns of absorption, biotransformation, and excretion of caffeine in humans and animals.

(2) Studies necessary to determine whether the teratogenic effects of caffeine seen in rats are caused by caffeine *per se* or by one of its metabolites, and whether any metabolities of caffeine that are unique to humans are teratogenic in appropriate animal models.

(3) Multigeneration reproductive and neurobehavioral studies in appropriate animal models to resolve questions about the effects of prolonged exposure to caffeine on the mammalian nervous system. Questions related to reproduction include the significance of testicular atrophy reported in rats and other potential reproductive effects. Neonates and adult rats from this study should be examined by various procedures for evaluating neuropharmacological effects and functional behavioral effects such as altered conditioning response, summary reflexes, continuous motor activity, and neurochemical analysis.

(4) Definitive chronic feeding studies in two appropriate species that will be adequate to resolve questions that have been raised about the potential carcinogenicity of caffeine. Sponsors of ongoing chronic feeding studies of caffeine in rats shall submit details of the design and conduct of these studies to the Food and Drug Administration so that it can be determined whether they meet current standards for long-term feeding studies and will satisfy the requirements of this regulation. If ongoing studies are determined to be inadequate, additional carcinogenicity studies will be required.

(5) Chronic feeding studies to determine whether caffeine can cause chronic, pathologic effects other than cancer.

(6) Appropriate epidemiology studies on caffeine performed in accordance

[1] Copies may be obtained from: National Academy of Sciences, 2101 Constitution Ave., Washington, DC 20037.

with the epidemiology guidelines of the Interagency Regulatory Liaison Group, which may be obtained from: FDA/ Bureau of Foods (HFF–330), 200 C St., SW, Washington, DC 20204.

(7) Appropriate studies demonstrating the technical effect for which added caffeine is used in soda water and other foods.

(f) Interested persons shall agree in writing to undertake the studies, or submit the information, referred to in paragraph (e) of this section by (60 days after date of publication of the final regulation in the **Federal Register**). Continued use of caffeine is contingent on the timely filing of adequate progress reports of such tests as specified in § 180.1(c)(3) and no indication of an increased risk to public health during the test period.

PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE

§ 182.1180 [Revoked]

2. Part 182 is amended by revoking § 182.1180 *Caffeine.*

Interested persons may, on or before December 22, 1980, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments. The comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Dockets Management Branch, Food and Drug Administration.

Dated: October 16, 1980.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Note.—Incorporations by reference were approved by the Director of the Office of the Federal Register on July 10, 1973 and June 27, 1977, and are on file in the Federal Register Library.

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